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BENIGN PAROXYSMAL PERITONITIS *

By SHEPPARD SIEGAL, M.D., *New York, N. Y.*

THE purpose of this paper is to describe in detail an unusual clinical syndrome which is at present little understood and often undiagnosed. The characteristics of this disorder are constant and distinctive.

The syndrome is characterized by recurrent paroxysms of severe abdominal pain with fever which may be as high as 105° F. Chilliness or a shaking chill may accompany the attacks. Involvement of the peritoneum is indicated by the subjective symptom of marked abdominal soreness and the objective finding of widespread, exquisite direct and rebound tenderness. On occasion true involuntary spasm of the abdominal wall may be noted. These abdominal signs are often so striking that to the surgeon they suggest an acute abdominal peritonitic lesion. Emergency operation has been repeatedly urged.

Chest pain of a pleuritic type is frequently present at some stage of the attack. Marked malaise, severe prostration, intense nausea and vomiting are almost constant characteristics. Diarrhea is conspicuously absent. Leukocytosis is a frequent finding. An occasional case may show urticarial wheals during the acute episode. This disease affects young people, often beginning in the second or third decade and continuing for many years. Nevertheless, they remain in good general health and their disorder, essentially benign, continues without the development of any persistent anatomical lesion and without permanent impairment of any physiologic function.

Although cases of an essentially similar nature have been previously described, emphasis has heretofore been laid upon the florid manifestations of erythema and purpura. This has tended to obscure the fundamental clinical picture of a disease which usually runs its course without skin eruption of any kind and with no bleeding tendency whatsoever. To draw attention to its distinctive clinical features, the term "benign paroxysmal peritonitis" is suggested until such time as classification becomes possible on a sound etiologic or pathologic basis.

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From the Medical Services, Mt. Sinai Hospital, New York.

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Included in this report are five new cases observed by the author. These are presented in clinical abstract and in table 1 as cases 1 to 5. In addition, data on five similar and probably related cases from the literature are tabulated in table 2 as cases 1 to 5. More detailed reference to two of these is made in the text.

Case Reports

Case 1. A 38 year old white man stated that his illness began at the age of 13, with an attack of chest pain accompanied by fever of 104° F. From then until about the age of 27 such episodes recurred at intervals of one or two months. In each attack there was chest pain, often bilateral, worse on inspiration. Each episode was febrile, the patient being acutely ill, prostrated and incapacitated for from three to five days. Pleurisy or pleurodynia was diagnosed repeatedly. It is not certain that a friction rub was heard. Localized areas of chest wall tenderness were frequently noted.

From the age of 18, occasional attacks were associated with abdominal pain. At the age of 27 the abdominal pain became and remained the dominant feature in all attacks. At first generalized, it localized after some hours in the right lower quadrant. Marked direct right lower quadrant tenderness was present and the diagnosis of acute appendicitis was made repeatedly. Diffuse abdominal tenderness, both direct and rebound, was invariably noted, occasionally accompanied by definite spasm of the right rectus muscle. Nausea, vomiting, constipation and intense malaise were typical of these attacks. Chest pain might occur as the abdominal distress subsided. It was the occurrence of this "pleurisy" which convinced him of the essential identity of the two kinds of attacks and led him to refuse all offers of operation. During an attack a white blood cell count of 16,500 with 70 per cent polynuclears was found. In none of the paroxysms were any skin lesions ever observed and there was never any evidence of gastrointestinal bleeding.

Neither the patient's past nor personal history shed any light upon the nature of his peculiar illness. He appeared to be well-adjusted, absorbed in his work and without overt neurotic trends. The family history was of interest only in that a maternal uncle had bronchial asthma. None of the patient's five siblings had had any allergic manifestation or any disease similar to that from which the patient suffered.

For more than nine years this patient's abdominal attacks continued, at intervals varying from two weeks to three months. In the intervals he remained quite well, except for occasional slight abdominal discomfort.

In an effort to ascertain the cause of his disease several complete investigations were made and the patient underwent a careful interval exploratory laparotomy. Complete roentgenographic studies of the gall-bladder, the gastrointestinal and genitourinary tracts were negative. Chest roentgenograms and an electrocardiogram were normal. Blood urea nitrogen was 17 mg. per cent, glucose 75 mg., cholesterol 180 mg. with ester fraction 120 mg., phosphorus 3.5 mg. and calcium 9.9. mg. Heterophile antibody reaction was positive only in 1:8 dilution. Brucella agglutination was negative. Blood Wassermann reaction was negative. Sedimentation rate of red cells was normal during and between episodes. Interval blood count: hemoglobin 96 per cent, white blood cells 8,500, polymorphonuclears 66 per cent, lymphocytes 29, mononuclears 4, eosinophiles 1 per cent. Bromsulfalein test of liver function showed no retention in 30 minutes. Gastric secretion curve was normal. Stool and urine examinations were normal.

At the interval operation no lesion was found to account for the patient's attacks. Small bowel lesions, Meckel's diverticulum and mesenteric adenitis were especially sought for. An appendectomy was performed, but despite this the patient's attacks continued unchanged.

TABLE I

Benign Paroxysmal Peritonitis

Case No. — Age — Sex	Age at Onset	Attacks: Duration — Interval	Fever	Symptoms — Signs	WBC — Differential	Allergy: Personal — Familial	Allergy: Skin Tests	Operations — Food Trials — Skin Lesions
1. 38 M	13 (27)	3–5 days — 3–12 weeks	103–104° F.	RLQ pain Direct and rebound tenderness Spasm Chest pain	16,500 Pmn 70% Eos. 0%	Negative — Uncle: asthma	Negative	Interval laparotomy neg.; appendectomy. — Food trials neg.; no skin lesions
2. 36 M	27	1–3 days — 1 week to 4 months	100–102.6	RLQ, LLQ pain Direct and rebound tenderness Chest pain	19,000 Pmn 90% Eos. 0%	Negative — Mother, sister: G.I. allergy Uncle: asthma	Liver, pork plus-minus	Hyperemia of visceral peritoneum. Food trials neg. Isolated wheals. Previous appendectomy.
3. 18 M	13	2–4 days — 5 days to 2 weeks	102–103	Generalized pain Direct and rebound tenderness Chest pain	18,000 Pmn 65% Eos. 0%	Ragweed hay-fever — Uncle: hayfever	Ragweed and house dust: four plus Foods: plus-minus	Appendectomy. Food trials neg. No skin lesions.
4. 37 M	25	3–7 days — 1–6 months	103–104	RUQ pain Direct and rebound tenderness Chest pain	12,700 Pmn 76% Eos. 0% Interval Eos: 0–7%	Negative Uncle: hayfever	Fish: two plus Other foods plus-minus	No operation. Partial food trials negative. No skin lesions.
5. 38 M	18	1–3 days — 1 week to 6 months	102–105	RLQ pain Direct and rebound tenderness Spasm Chest pain	13,250 Pmn 84% Eos. 0% Interval Eos.: 0–9%	Negative — Negative	Negative	No operation. Partial food trials negative. No skin lesions. Recurrent febrile rheumatism.

TABLE II

Benign Paroxysmal Peritonitis
Similar Cases from the Literature

Case No. — Age — Sex	Age at Onset	Attacks: Duration — Interval	Fever	Abdominal Symptoms — Signs	WBC — Differential	Allergy: Personal — Familial	Allergy: Skin Tests	Operation — Food Trials — Skin Lesions
1. 26 M	2	1–2 days — 1 week	103° F.	Generalized pain; tenderness, left more than right; spasm	17,000–27,000 Eos. 0–24%	Pers. H. neg. Family H. neg. Brother of Case 2	Scratch tests neg.	Splenectomy Appendectomy — Occasional purpura. Cause undetermined
2. 24 M	4	several days — 1–6 weeks	103	Generalized pain; tenderness; spasm	15,000–20,000 Eos. 7%	Pers. H. neg. Family H. neg.	N.R.	No operation — Occasional petechiae Recurrent rheumatism Cause undetermined
3. 29 M	22	several days — 1–4 weeks	102.6	RUQ pain; tenderness; spasm	24,000 Eos. 2%	Pers. H. neg. Mother—hay fever	Foods neg.	Appendectomy — Erythema. Cause undetermined
4. 31 F	30	several days — attacks "frequent"	100.4	Generalized pain; tenderness; spasm	11,5000 Pmn normal Eos. 0%	Hay fever Family H. not given	Wheat pos.	Urticaria of skin and visceral peritoneum — Improved with elimination of wheat
5. 24 F	2 weeks	1–2 days — 1–10 weeks	104	Generalized pain; tenderness; spasm	29,000 Eos. 0%	Pers. H. neg. Family H. neg.	Neg.	Appendectomy — Proved milk allergy — No skin lesions

Thorough studies were made for a possible allergic cause of this patient's illness. Intracutaneous tests were essentially negative, showing only suspiciously positive reactions to pepper and garlic. Greatly restricted trial diets had no influence upon his symptoms. A food diary yielded no information. Subcutaneous histamine given three times weekly in ascending dosage to the limits of tolerance over a period of several months was without observable effect. However, the patient appeared convinced that the use of ephedrine sulphate three times a day diminished the frequency of his attacks during the year preceding this report.

Case 2. This was a 36 year old white man whose attacks of abdominal pain began at 27 and had occurred since then at intervals of one week to four months. In each attack there was severe, usually cramplike pain and tenderness, both more marked in the lower part of the abdomen, nausea and vomiting, constipation, leukocytosis from 13,000–19,000, with 80–90 per cent polynuclears, and fever varying from 100–102.5° F. On examination during the paroxysm rebound tenderness was usually striking, distention was slight, spasm absent. The acute phase of the attacks lasted from 12 to 24 hours, but it was two to three days before most of the abdominal tenderness and the prostration subsided. Localization of pain and tenderness was most often in the right lower quadrant though pain might begin in the left side of the abdomen.

After one year of illness the patient noticed the occurrence of chest pain of a pleuritic type which followed the major abdominal phase. Shift of tenderness from the lower abdomen to the right upper quadrant often with accompanying rib tenderness heralded the onset of this "chest stage." Referred shoulder pain and aggravation of pain upon inspiration or with the recumbent position were the usual accompaniments. No friction rub was heard.

With many of the abdominal attacks, and occasionally between them, discrete wheals were noted on the face or forehead. No generalized urticaria occurred. On one occasion, following severe vomiting, many tiny petechiae were seen in the eyelids. No gastrointestinal bleeding had ever been observed.

Between attacks the patient was usually completely well. However, minor abortive manifestations might occur, such as a sense of great exhaustion with abdominal crampiness and distention. At such times facial pallor and an urticarial wheal might be noted. These phenomena might presage a major episode or might pass off altogether after a few hours. The frequency of the attacks had not changed appreciably in recent years, although they appeared somewhat less intense.

One year after the onset of his illness an exploratory laparotomy was performed during a mild attack with negative findings insofar as any gross lesion was concerned. But the surgeon noted that: "The bowel lying in the lower abdomen and pelvis showed evidence of peritonitis manifested mainly by definite but moderate injection which involved equally the cecum, the ileum and the sigmoid. There was no exudate or fibrin."

The patient's past history included two brief episodes of dry pleurisy in early youth, chronic and recurring acute sinusitis, less severe in recent years, and acute appendicitis with appendectomy four years before onset of the present illness.

The family history was of particular interest. His sister had recurrent severe non-bloody diarrhea for five years. This was believed psychogenic until careful food trials discovered the existence of allergy to wheat, chocolate and coffee. Complete cure for the preceding six years followed exclusion of these foods. The patient's mother had known ever since childhood of a gastrointestinal reaction to uncooked apple. A maternal uncle had bronchial asthma.

Intradermal skin tests were negative and prolonged diet manipulations failed to demonstrate a specific food factor. The most stringent diets did not prevent the occurrence of attacks. The patient had undergone repeated investigations of every pertinent kind: roentgen-ray studies of the gastrointestinal and genitourinary tracts

and of the gall-bladder were negative. Roentgenograms of spine and chest were negative. Blood agglutinations for Brucella, typhoid and paratyphoid and for typhus fever were negative. Blood chemical studies including urea nitrogen, glucose, calcium, phosphorus, sodium, potassium, and magnesium were within normal limits. Blood cholesterol was 370 mg. per cent. Interval blood counts were normal. Blood sedimentation rate during and after the attacks was normal.

Attempts to abort attacks with adrenalin and ergotamine tartrate failed. Ephedrine sulphate taken regularly for several days did not prevent an acute attack. Nicotinic acid orally in 200 mg. dosage at two to three hour intervals appeared on one occasion to delay but did not prevent a paroxysm.

Case 3. This was an 18 year old white male who in early childhood had an attack of severe pain in the right side of the chest and abdomen accompanied by fever. He was then well until the age of 13 when he had another similar attack lasting several days and he recalled that it was painful to move or walk. It was thought he might have had a gall-bladder attack. Six months later another attack occurred and then more and more frequently. Recently the interval between attacks had been only two weeks and for a short time they occurred every five days.

Description of an average episode is as follows: for almost a full day there was a prodromal period characterized by a sense of sluggishness and of being worn out. Pain appeared diffusely across the whole abdomen, often radiating into the flanks or even to the left shoulder. Pain might begin in either side of the abdomen. Nausea was usual but vomiting uncommon during the attacks. The temperature usually rose to 102° to 103° F. Abdominal tenderness, direct and rebound, was marked. Throughout the attack and for one or two days afterwards the abdomen was sore and walking painful. The duration of each episode was two to four days. In the preceding few years there was no chest pain at all. Leukocytosis as high as 18,000 had been present, but the polymorphonuclears numbered only 64 per cent. Eosinophilia was never observed. No skin eruption or bleeding tendency was ever noted. Between attacks, each of which was acute and completely disabling, this patient was altogether well.

One year before his admission to the Mt. Sinai Hospital an appendectomy was done, without thorough exploration. Ten days later the patient had one of his usual attacks and they continued to recur as before. Despite careful roentgen-ray investigation and blood studies, chemical, serologic and hematologic, nothing was found which offered a clue as to the cause of this patient's illness. Blood urea nitrogen, glucose, cholesterol, phosphatase, amylase, blood culture, bile culture, and spinal fluid studies were all within normal limits. Duodenal drainage was negative. Fragility of red blood cells was normal. Hemoglobin was 98 per cent, white blood cells 1,200, with normal differential. Blood sedimentation time (Linzenmeier technic) over two hours for 18 mm. fall.

This patient had developed typical ragweed hay fever in the preceding two years. Skin testing showed four plus reactions to ragweed and to dust but food tests were negative other than one plus responses to grape, pineapple and cucumber. A paternal uncle had ragweed hay fever, the family background as to allergy being otherwise negative.

Repeated clinical testing with the suspected foods did not precipitate any abdominal attacks. Careful food diary, repeated trial diets and forced feedings failed to establish a definite relation between the ingestion of certain foods and the occurrence of the patient's attacks.

Unfortunately the patient lapsed from observation before the effect of any pharmacologic agents upon his attacks could be determined.

Case 4. The patient was a 37 year old white male. For 12 years he had had recurrent episodes of fever, abdominal and chest pain, nausea and vomiting. During

this time he had had six hospital admissions, including a stay at the Mayo Clinic, in an effort to unravel the mystery of his disease. He had had practically every conceivable type of investigation which might have any bearing upon his disorder.

The patient's attacks generally followed this pattern: There was usually a prodromal period in which he felt some general malaise and a sense of being "let down." The attack itself began with epigastric or left upper quadrant pain, often cramplike in nature. This increased somewhat in severity and at the same time the patient felt chilly or might even have a shaking chill. His temperature rose usually to 103° or 104° F. The pain tended to shift toward the right upper quadrant where it finally localized. It was often noticeably aggravated by breathing and might then be accompanied by right shoulder pain. The patient was moderately prostrated and usually had to remain in bed three to six days.

Physical examination during the attack revealed quite marked right upper quadrant tenderness without definite spasm, at times slight tenderness over the lower ribs on the right, both anteriorly and posteriorly. His signs had never been such as to suggest a need for urgent operation. Because of the localization of the patient's symptoms and signs in the right upper quadrant, the diagnosis of acute inflammation involving the gall-bladder or the right kidney had been made most often. However, several complete roentgen-ray studies of both gall-bladder and urinary tract were negative. On several occasions diaphragmatic pleurisy was suggested. No pulmonary signs were ever present. A pleuritic friction rub was not usually observed but, according to the patient, had been noted on one occasion.

Roentgenograms of the chest and complete gastrointestinal workup on several occasions were normal. Repeated blood cultures, urine cultures, stool cultures, and cultures of sinus washings revealed no significant organism. Numerous smears for malarial parasites and a variety of serologic reactions (Wassermann, heterophile, agglutination for typhoid, paratyphoid and Brucella, and Felix-Weil) were negative. Blood chemical studies including total protein determination were normal as were routine urine analyses and most blood counts. On one occasion during an attack the white cell count was 12,700 with 76 per cent polymorphonuclears. A single blood count while the patient was well showed 7 per cent eosinophilia. During this admission sternal marrow and muscle biopsy were both normal.

Because of the unusual character of the patient's illness and the difficulty in arriving at a satisfactory diagnosis, he was suspected of a profound psychoneurosis or of being an outright malingerer. In the hospital he was closely observed while having his temperature taken and it was found that the temperature rises were genuine. In a recent evaluation of his personality by a competent psychiatrist, it was concluded that although he might have emotional difficulties it was extremely unlikely that psychogenic conflicts had any bearing on his illness.

In his personal, past and family history only the following appeared pertinent. In childhood he had had two or three episodes of pleurisy with fever. A maternal uncle had hay fever. From the allergic point of view, skin tests revealed only slight positive reaction to flounder, chocolate, pepper, onion, and tea. These skin reactions had no significance as judged by careful clinical trial. This patient, however, was not coöperative enough to exclude food allergy as a possible cause of his disease. The effect of adrenalin or other agents upon his attacks is not known.

It is an amazing fact that after 12 years of illness he was otherwise quite well. The only evidence of progression of his disease was that whereas at first his attacks occurred only two or three times a year, they had become monthly occurrences. Between attacks he might feel entirely well or he might be troubled by slight abdominal discomfort or malaise. He had lost no weight and had been able to carry on his job.

Case 5. This was a 38 year old white man who at the age of 12 had had an

attack of abdominal pain diagnosed as acute appendicitis, with three recurrences yearly for three years thereafter. For an interval of three more years he was prone to repeated episodes of fatigue, nausea and a shaking chill without abdominal pain. From about the age of 18 to the time of admission, abdominal pain had again become the outstanding symptom. A typical paroxysm would begin gradually with a sense of pressure in the right lower quadrant, spreading over much of the abdomen. Tenderness and pain followed, which likewise usually started in the lower abdomen and spread upward. The pain remained severe for 18 to 24 hours, but general abdominal soreness persisted for two to three days after the acute stage had passed The temperature often rose as high as 102–103° F., and might even reach 105° F. The febrile stage did not usually last longer than 24 hours. Nausea was frequent, vomiting occasional. Diarrhea was consistently absent, the bowels being constipated or regular. The patient was usually confined to bed for one or two days. During the attack there was usually a sharp loss of weight. The patient had never at any time observed skin lesions of any type or bleeding tendency of any kind.

Ten years previously the frequency of the attacks increased to every two months and more recently they became still more frequent so that in the preceding 12 months the patient had had 22 major paroxysms. As a result the free interval was often only eight days. The longest interval had been six months, which occurred six years ago. Despite the intensity of the paroxysms and their increasing frequency, the patient felt well and vigôrous, retained a good appetite, maintained his weight and, though handicapped, was able to carry on his business actively.

In one out of every five attacks the pain localized ultimately in the right upper quadrant and took on a pleuritic character, being distinctly aggravated by breathing. Pain in the right shoulder might then be present. Because of the sharpness of the pleuritic type of pain the patient was unable to lie down or sleep. This syndrome might last three days.

The physical findings during an attack, or shortly after, are described in the following note taken from the report of the Consultation Service at Mt. Sinai Hospital: "The patient had an attack of pain in the right upper quadrant and lower right chest last night. The pain was more marked on inspiration. His temperature was 100° F. (p.o.). Physical examination reveals rigidity and tenderness in the right upper quadrant. Jarring of the chest causes pain in the right upper quadrant. There was also slight rigidity of the right lower quadrant. Fluoroscopy showed both leaves of the diaphragm to move well.

"The negative gall-bladder roentgen-ray, the history of previous attacks beginning with pain across the lower quadrants and shifting after 24 hours to the upper abdomen and accompanied by nausea and fever suggest that the attacks were caused by recurrent appendicitis. The presence of abnormal signs in the right upper quadrant suggests that we are dealing with an infrahepatic inflammatory process which is best explained on the basis of an appendicitis with the appendix situated high in the abdomen."

The surgical consultant agreed with the above opinion and advised exploratory laparotomy.

It is evident that the acuteness of the abdominal findings during this patient's paroxysms was such as to simulate closely an acute surgical abdomen. He refused operation and at the time of this report he had not been explored either in a free interval or during an attack.

In 1936, 1937, 1938, 1939, 1940 and again in 1944 the patient had repeated roentgenographic and other studies. Gastrointestinal series, cholecystogram, barium enema, intravenous pyelogram and flat plates of chest and abdomen were all negative. Basal metabolic rate was − 3 per cent. Electrocardiogram was normal. Blood Kahn reaction and agglutination tests against brucella were negative. Blood non-protein

nitrogen, uric acid, glucose and icterus index all were within normal limits. Gastric secretion curve and biliary drainage were normal. Stools were negative for occult blood and ova and parasites. Malarial smears were negative. Blood counts between episodes were usually normal. Hemoglobin was 104 per cent, red blood cells 5,200,000; white blood cells 11,200, polymorphonuclears 64, lymphocytes 30, monocytes 3, eosinophiles 2, basophiles 1. However, on several occasions a moderate eosinophilia was noted, usually from 5 to 9 per cent. Ear, nose and throat and neurological examinations were negative. During the attack a moderate leukocytosis might occur; on one occasion white blood cells numbered 13,250 with 84 per cent polymorphonuclears, and eosinophiles 1 per cent. Intradermal skin tests were entirely negative.

The family history was quite negative for anything related to the patient's illness. There was no history of allergy. The patient's past history was noncontributory, but included another peculiar syndrome which, though not chronologically related to his abdominal attacks, was obscure enough to bear some possible relationship to them. From the age of six to 12 he suffered daily pains in the calves of his legs. There was a free interval until the age of seventeen and since that time he had had pains in the ankle, heel, calf, knee or lower thigh. Usually there was no swelling though the ankle might swell slightly. The ankle or knee might become quite red and feel warm to the touch. Chilly sensations usually accompanied these symptoms and, particularly in recent years, the temperature might rise to 101–102° F. The attack lasted three to four days. No similar involvement of the upper extremities occurred. These rheumatic attacks bore no chronologic relation to the abdominal paroxysms. They might be precipitated by striking the leg against some object, and early strapping with a snug elastic bandage appeared to ward off an attack. The usual interval between episodes of this unusual form of rheumatism was two to three months.

A recent brief trial with ephedrine sulfate did not abort an abdominal attack. Three injections of epinephrine likewise failed to modify the course of a typical paroxysm. Experimentation with elimination diets did not prevent the abdominal paroxysms but the patient had not yet submitted to a period of observation with careful trial diets coupled with study of a food diary.

The Clinical Syndrome

1. Onset, Course, Age Group, Frequency and Duration of Attacks. Onset of this disease has been in the second or third decade in all five cases (table 1). Although all the cases here presented occur in men, the author has been informed of an instance of this disorder in a young woman.

Early in the course of the illness acute episodes may occur only once or twice yearly, but sooner or later a more frequent cycle is established varying from once a week to once a month. Longer free intervals may separate rapidly recurrent series of paroxysms. Occasionally even after the disease is well established, a free interval of several months may ensue and without apparent cause. There appears to be little tendency to spontaneous improvement and in several cases a greater frequency of attacks was noted in the later years. The disease continues for many years, the average duration for this series being approximately 14 years. One of these patients had had attacks for 25, another for 20 years. The duration of individual episodes is usually two to three days, though more severe attacks may disable the patient for almost a full week. The febrile stage does not usually last more

than 24 hours. The relationship of fatigue, exertion, worry and other overt psychological factors to the attacks is debatable.

2. Abdominal and Chest Pain. Abdominal pain is one of the essential symptoms. At first it may be diffuse and cramplike or on the other hand it may be localized in the upper or lower abdomen with a steady and gnawing character. Localization is prone to occur in the right side of the abdomen, especially in the right lower quadrant, as in four of the five cases. Abdominal soreness rather than actual pain may sometimes be the first indication of an attack, preceding the occurrence of actual pain. When the upper abdomen is involved, the pain often takes on a pleuritic character and is accompanied by pain in the shoulder, thus suggesting diaphragmatic irritation. In three cases (1, 2, 5) lower abdominal tenderness spread upward in occasional attacks and led to a chest phase almost distinct from the first or abdominal stage. At these times marked chest wall tenderness was elicited. No friction rub or pulmonary signs were audible.

In case 1 recurrent "pleurisy" was present for years before abdominal pain appeared as the primary symptom. These paroxysms of chest pain were accompanied by fever rising to 103 or 104° F. After 14 years the patient became subject to bouts of abdominal pain with a syndrome identical with the other cases.

3. Fever. Fever is characteristic of the disease. On rare occasions an attack may be afebrile, but some fever is an almost invariable accompaniment. Most often there is an abrupt rise to 102° or 103° F., but the temperature may even reach 105° F. and with a shaking chill. Occasionally the febrile paroxysms may be the predominating clinical feature and the patient be closely studied as a case of "fever of unknown origin" (case 4). The duration of the fever is usually not more than 24 to 36 hours. A slight secondary rise may accompany the 'chest phase' as in cases 1, 2 and 5.

4. Abdominal Signs. Marked direct and rebound tenderness are characteristic of the acute abdominal crises. They are indicative of the underlying peritoneal irritation. At first localized and most often in the lower abdomen, these signs become almost generalized throughout the abdomen. Some abdominal soreness persists for two to three days. The patient often walks in a typically stooped posture to relax tension upon the tender abdomen. This may be noticeable at the very beginning of an acute episode. Distinct spasm of the abdominal wall has been noted at times in two of the cases, 1 and 5, thus completing the picture of a "surgical abdomen." It was absent in the other cases. Moderate abdominal distention may be present.

5. Systemic and Gastrointestinal Manifestations. Marked prostration and malaise characterize the acute phase. A sense of profound exhaustion may precede the actual onset, or may be the chief symptom of an abortive episode in association with abdominal crampiness and distention. General muscle achiness and actual muscle soreness may follow an attack.

In one instance, case 5, an apparently independent and quite obscure syndrome of lower extremity pain and fever recurred for many years. This peculiar form of rheumatism was characterized by brief episodes lasting only two or three days. The knees and ankles were especially affected. The joints became painful, tender and occasionally reddened areas appeared and the joint might even be slightly swollen. These rheumatic attacks did not occur in any definite relation to the abdominal paroxysms. However, both began at about 18 years of age and continued to the present. It should be noted that this unusual rheumatic syndrome differs from rheumatic fever, rheumatoid arthritis, gout and from the more recently described palindromic rheumatism. Its possible relationship to the major abdominal syndrome is discussed later.

Nausea, vomiting and belching are usually present during an acute episode. During the attack the patient is almost always constipated. Diarrhea does not occur as part of these paroxysms. At times profuse salivation may be noted at the onset of an attack.

Considerable weight loss, as much as five to 10 pounds, may occur in severe attacks and is quickly regained. Despite years of repeated illness these patients do not lose and may even gain in weight. They remain robust and manage to lead busy lives despite their physical handicap.

6. Skin Manifestations. In four of the five cases no eruption of any kind was observed. A grayish facial pallor might be noted just before and during the acute episode. However, in case 2 one or two urticarial wheals might accompany a major paroxysm, or might occur together with other symptoms of an abortive attack. These wheals were most often situated upon the face or forehead. In this case, too, typical crises occurred without any skin manifestation. As will be discussed later, the vascular skin lesions, as in case 2, are of fundamental interest towards an understanding of the nature of this disease, but they are not an essential part of its clinical picture.

7. Hematologic Findings. All five cases showed a rise in total white blood cell count during some paroxysms, though this was not invariable. In case 2 the rise was most marked, to 19,000, and accompanied by considerable polynucleosis, 90 per cent. In others no noticeable polymorphonuclear increase occurred. In none was eosinophilia noted during an acute attack, although in two cases eosinophile counts, higher than normal, were occasionally present during a free interval (cases 4 and 5).

8. Allergic Study. Of the five cases, four gave a positive family history of allergy. In case 2 this was particularly in the form of gastrointestinal reactions to food. Case 3 was himself clearly allergic, having ragweed hay-fever. In none of the other cases was there any personal allergic history.

Intradermal testing with food extracts was done carefully in all five cases. In cases 1, 2, and 5 these were either entirely negative or showed only plus-minus reactions. In cases 3 and 4 slight positive reactions to foods were

of no clinical significance. In case 3 marked reactions to ragweed and house dust were present and were of significance for the patient's nasal symptoms.

Careful investigation by means of trial and addition diets in cases 1, 2 and 3, failed to reveal causative food factors. In cases 4 and 5 this was still to be carried out in an exhaustive manner, though elimination diets yielded no information in case 5.

9. Operative Findings. In only one of the five cases (case 2) was laparotomy performed during an acute paroxysm. In this instance the sole finding was definite injection of subserosal vessels of the visceral peritoneum in the lower abdominal cavity. In this case appendectomy had been performed for acute appendicitis four years before the onset of the present illness. In two other cases (1 and 3) appendectomy did not affect the course of this disease. Careful interval exploration in case 1 revealed no intra-abdominal lesion whatsoever. No laparotomy was done in cases 4 and 5.

Pathology and Etiology

The clinical characteristics of this syndrome offer a clue to its fundamental pathologic mechanism. It may be fairly assumed from its prolonged course punctuated by febrile paroxysms that the essential lesion consists of some form of acute readily reversible inflammatory reaction. Certain observations indicate more precisely the probable nature of this reaction. Thus, the association of urticarial wheals with the attacks in case 2, together with the operative finding in the same case of hyperemia of the visceral peritoneum in the lower abdomen point to a vascular response of dilatation and hyperpermeability.

From the available clinical evidence the site of this vascular reaction may also be postulated. The outstanding physical findings are those of marked peritoneal irritation, which coincides with such operative findings as are at present available. Thus, the tissue reaction which gives this disease its distinctive clinical character takes place in the visceral peritoneum. Whether this is the primary site of reaction or whether it is secondary to an intestinal mucous membrane response cannot be stated. An enteritis alone would not produce the marked direct and rebound tenderness which are invariably present. Furthermore, diarrhea would be an expected symptom and this is invariably absent during the typical paroxysm.

Although the disease may well be enteric in origin, it might be conceived of as an unusual form of recurrent acute serositis. The history of paroxysmal chest pain in case 1 which preceded the abdominal syndrome by several years, and the unusual rheumatism in case 5 suggest that the pathologic process may involve other serous membranes as well as the peritoneum.

The suggestion that this syndrome has its basis in a form of vascular disease prompts speculation as to its possible relation to other systemic vascular disorders. Attention logically focuses first upon the "Erythema

Group" of Osler within whose broad category at least one case similar to those in the present series may be found. Thus, in Osler's very first paper on the visceral complications of the erythema group,[1] case 1 possesses many of the ear-marks of this syndrome: a man of 27 who for eight years had attacks of severe abdominal pain, vomiting and fever followed by abdominal soreness. Skin erythema, a prominent finding at first, was absent in the last two years of observation. All diagnostic procedures then available were negative.

Again in a later paper [2] Osler notes with respect to the gastrointestinal symptoms of visceral erythema that "the manifestations may be for years abdominal without skin eruptions." On the other hand it should be noted that within the "Erythema Group" are included cases characterized by gross hemorrhage from the kidneys and gastrointestinal tract, by termination in uremia, or by endocarditis, pericarditis and an ultimately fatal, febrile course. Such clinical phenomena appear altogether foreign to the syndrome here described. More recent clinical contributions to the study of the visceral manifestations of cutaneous erythema fail to shed light upon the present problem.[3, 4] It may be suggested that just as other diseases, notably acute lupus erythematosus, have been split off from the general category of Osler's erythema, so too this disorder now warrants separate classification.

The association of abdominal pain with angioneurotic edema, particularly of the familial type, was likewise given particular emphasis by Osler.[5] Single episodes of great severity and simulating acute intestinal obstruction have been described.[6] However, the occurrence in the course of angioneurotic edema of a syndrome of the type here described has not been reported.

Abdominal pain is a primary characteristic of Henoch's purpura.[7] In most case reports isolated acute attacks of considerable violence are reported, which simulate an acutely inflamed abdomen,[8] but evidence of gross gastrointestinal bleeding is usually present,[9] and actual cutaneous purpura occurs, though it may be delayed. Renal involvement, a frequent characteristic of Henoch's purpura which often leads to a fatal issue, likewise distinguishes that disease from the present syndrome.

As with other varieties of the "Erythema Group" Henoch's purpura includes certain cases of a milder type which tend to be of prolonged duration with repeated attacks. In such cases the element of purpura may be so slight as to raise the question whether one is dealing with the same disease. Evidence of visceral bleeding is likely to be absent altogether. Althausen, Deamer and Kerr,[10] in an excellent paper, "The False Acute Abdomen: Henoch's Purpura and Abdominal Allergy," have described several such instances. The clinical features of four of these are of the greatest interest for an understanding of the present syndrome. They are included as cases 1 to 4 in table 2. Three of these closely approximate the clinical picture of the disease here designated as benign paroxysmal peritonitis. They are

characterized by recurrent attacks over many years of severe abdominal pain and tenderness with high fever and leukocytosis. In two instances the paroxysms had continued for 20 and 24 years ever since onset in very early childhood. These two patients were brothers. In the third case the duration was seven years at the time of publication.

The first two cases exhibited rather mild cutaneous purpura on a few occasions but otherwise the attacks were without skin eruption. In case 3 erythema was a frequent accompaniment of the acute episodes, but no purpura occurred. Interval eosinophilia was present at times in cases 1 and 2 just as has been observed in cases 4 and 5 of the author's series. Marked leukocytosis and polynucleosis were characteristic of the acute attack in each of these cases. In contrast with the present group, however, spasm of the abdominal wall appears to have been a striking finding.

Another interesting parallel is offered by the second case in which recurrent pain in the ankles and knees, occasionally with redness, was present between 11 and 20 years of age. This resembles the similar syndrome in case 5 of the author's group. In neither case was there any direct relation between these attacks and those affecting the abdomen but the Henoch-Schoenlein pattern is evident and it appears probable that this peculiar form of rheumatism is another manifestation of the same underlying disorder.

In none of these three cases which parallel the present syndrome most closely was it possible to establish any definite cause or to influence the general course of the disease. The fourth case, taken from the same paper, presents a syndrome very similar to the one under discussion. However, this patient's disease was of a comparatively short duration. A temperature rise was apparently noted on but one occasion. The operative finding of urticaria of the visceral peritoneum makes this a case of particular interest.

Case 4 (*table 2*). A woman of 31 had suffered from childhood to the age of 14 from recurrent attacks of abdominal pain and vomiting. All her life she had been subject to urticaria, hay fever and hemorrhagic manifestations such as petechiae, bleeding from the gums, epistaxis and profuse bleeding from small cuts.

At the age of 30 the patient had an attack of severe epigastric pain, radiating to the back, with nausea, profuse salivation and drenching perspiration. The pain lasted several hours. Nausea and upper abdominal tenderness persisted for several days. Blood, urine, cholecystography and gastrointestinal series were all negative.

Six months before admission the patient began to have frequent similar though less severe episodes. For a while tincture of belladonna appeared to be of some value and atropine gave spectacular but temporary relief during an attack. Physical examination revealed marked abdominal hyperesthesia, general abdominal tenderness and rigidity, all more on the right side. Temperature was 100.4° F.; white blood cells 11,500; normal differential. Exploration of the abdomen disclosed small whitish papules on the visceral peritoneum, especially numerous over the appendix. Appendectomy was performed. Microscopic examination showed edema of the subserosal tissue. The attacks continued until later skin testing revealed sensitivity to several foods including wheat. With elimination of wheat products, the attacks have occurred only rarely and in a mild form.

This case differs from those of the author's series in having positive skin

reactions to foods, at least one of which was of apparent clinical significance. The marked improvement which evidently followed exclusion of the offending food factor warrants the conclusion that in this instance the abdominal syndrome was due to food allergy. Further consideration of abdominal allergy due to foods in relation to benign paroxysmal peritonitis is warranted in the light of these observations.

Gastrointestinal reactions due to food hypersensitiveness may be of acute or chronic types. The acute reactions are usually characterized by severe colic, nausea, vomiting and diarrhea. Often there is urticaria or angioneurotic edema as well. Such manifestations first described as forms of egg poisoning [11, 12] were also graphically presented in 1909 as a form of "Buckwheat Poisoning." [13] Despite the title, early experiments with skin testing are included, which revealed the exquisite skin hypersensitiveness to the specific food allergen which is typical of the acute, immediate gastrointestinal reaction. Additional cases with similar symptomatology have been described repeatedly.[14, 15, 16, 17] More violent reactions characterized by vasomotor collapse and even death have been observed.[18]

Purpura, clearly due to food allergy, has been described by Alexander and Eierman [19, 20] and also by Kahn.[21] In some of these cases abdominal pain was present, but none of them presented the clinical picture with which this paper is concerned. The presence of fever and marked abdominal tenderness, direct and rebound, constitute essential characteristics of this disorder. Few reported instances of food allergy include these phenomena. In this connection Rowe [15] states: "The fact that acute allergy may produce fever as well as leukocytosis must be kept in mind in differential diagnosis. Eosinophilia moreover is not necessarily present in allergy." He also cites a case illustrating the occurrence of fever and acute abdominal findings apparently as an allergic response to a specific food:

> "A man of 39 with increasing pain in the right side of the abdomen, particularly right upper quadrant, for 15 years. Distention, belching, canker sore, coated tongue. Appendectomy without results six years before. Spastic constipation and diarrhea.
>
> "Three years ago sudden severe left lower quadrant pain, great tenderness, increasing fever, leukocytosis indicating emergency operation. Diffuse congestion of intestinal coils in lower abdomen with considerable gray sterile fluid.
>
> "Later, idiosyncrasy to crab found responsible for similar though milder attacks. Gastrointestinal series, barium enema, stools, neg. Well for two years with elimination of several foods. Skin tests neg."

The operative findings in this case are reminiscent of those in case 2 of the present series and the clinical picture is similar. Because of the relative paucity of precise clinical data this case is not included in table 2.

As further support of his contention that fever may constitute an allergic reaction to food, Rowe quotes a colleague "who observed a patient in whom sensitization to milk produces a temperature of 105° F." He also cites a case of a lad of 19 with recurrent attacks of fever from 101 to 105° F. for several days every two to three months for 12 years. He became entirely well while under observation for more than two years on a milk-free diet.

Additional evidence for the occurrence of fever in allergic reactions to food may be derived from a report by Carr [22] in which there is rather briefly noted the development of fever as high as 102.4° F., together with headache, drowsiness and joint pains when a man of 35 was placed on a Sippy régime for duodenal ulcer. The symptoms subsided when the patient was taken off milk but the experiment was not repeated.

L. P. Gay [23] notes an instance of agonizing lower abdominal pain in a man of 40. Temperature of 102° F. and leukocytes to 17,000 were present. The abdomen was rigid, distended, with marked tenderness in both lower quadrants. The pelvic colon was palpable, spastic and very tender. The patient had had a severe gastrointestinal upset from pork two years before and the evening before this attack he had eaten pork sausage. The attack subsided spontaneously but a similar though mild episode followed the eating of cooked pork at a later date.

A more recent paper by Hampton [24] is concerned with Henoch's purpura based on food allergy. It includes one case which has some points in common with the syndrome under discussion. Thus, in addition to abdominal pain some febrile response was noted which disappeared when the suspected foods, eight in number, were finally eliminated from the diet. Skin tests were negative. Two features of this case differ from those here described: diarrhea was a striking symptom and the patient's attacks responded dramatically to hypodermic adrenalin.

Many of the above-cited examples of food allergy have features in common with the syndrome of benign paroxysmal peritonitis and some fairly closely approximate it. However, within the proved allergic group only one case, reported by Cooke,[25] presents the complete clinical syndrome. In this case cure was effected by exclusion of a single food, milk.

Case 5 (*table* 2). A young woman, age 24, suffered with recurring attacks which began when she was two weeks old. In early life the frequency was once a month, the longest period of freedom being 10 weeks. For a year the attacks occurred weekly. In each attack there was a prodromal period of uneasiness, anorexia and abdominal discomfort lasting several hours. Some mild attacks did not go beyond this stage. Next there was a crescendo period with rapid increase of prostration, abdominal colic and generalized pains. Fever, rising as high as 104° F., and leukocytosis as high as 28,800 were then present. No eosinophilia noted. The abdomen was rigid, with tenderness at times as extensive as in general peritonitis, but varying in the location of maximum sensitiveness. There was constant nausea, belching and vomiting. This stage lasted from eight to 16 hours and was followed by a period of rapid recovery. She then felt well and quickly regained the four or five pounds which she had lost in the attack. Exploratory laparotomy was done at the Johns Hopkins Hospital and the appendix removed. It was without effect.

Intradermal tests were entirely negative. The family history for allergy was negative. However, it was decided to exclude those foods most commonly taken from infancy onward. Hence milk, eggs and meat were eliminated from the diet. The attacks stopped. Milk was subsequently added to the diet on two occasions and the well recognized prodromal symptoms appeared at the end of two days. After these two experiences the patient could not again be induced to take milk. When last

seen, after a nine year follow-up the patient had been free of all attacks. She never touched milk and was not then willing to repeat the experiment.

The sudden cessation of attacks of 24 years' duration by the withdrawal of milk and the reproduction of mild attacks on two occasions by the use of milk seem to warrant the diagnosis of an allergy.

Despite the extremely early onset of the disease at two weeks of age the identity of clinical characteristics leaves little room for doubt that this case is an instance of the syndrome here discussed. The abdominal spasm is somewhat unusual, but similar to several of the cases observed by Althausen, Deamer and Kerr. This case proves that paroxysmal peritonitis, with high fever and leukocytosis can be caused by food hypersensitiveness.

Cooke's case possesses additional interest because it was originally published in 1908 by Janeway and Mosenthal [26] as "An Unusual Paroxysmal Syndrome Probably Allied to Recurrent Vomiting." These writers, then in complete ignorance of the cause of their patient's illness, made the following observations which logically apply to the whole syndrome of paroxysmal peritonitis: "It seems most unlikely that any inflammatory focus could continue for so many years to produce exactly similar attacks without leading to more serious consequences or giving other evidences of its existence." The clinical accuracy of this point of view is such that no attempt will be made to discuss obscure organic causes which could not possibly explain this unusual syndrome.

A further observation from the same paper is likewise pertinent to the present problem. "As for the ubiquitous diagnosis for all unexplained crises, hysteria, we think that scarcely warrants serious consideration. Hysterical pain is common, hysterical fever may exist, hysterical leukocytosis seems out of the question." It must be granted that in the light of present concepts of the psychosomatic causation of disease one cannot altogether exclude the possibility of a psychogenic component in this bizarre syndrome.

Certain observations in the author's series likewise provide support for the allergic theory. The clinical course of the disease fits well into the allergic category, for it is paroxysmal, benign, and its onset is in early life. The vascular dilatation and hyperpermeability which seem to comprise the essential lesion of this disease are likewise typical of the allergic response. The high fever alone does not suggest an allergic reaction. However, as has been shown, febrile reactions may be due to food allergy. It may incidentally be noted that other well established forms of allergic reaction such as serum disease are typically febrile.

Four of the five cases in the present series give a positive familial history for allergy. In case 2 this was particularly of the gastrointestinal type. Case 3 is himself clearly an allergic individual. Another possibly significant observation is the occasional interval eosinophilia noted in cases 4 and 5. All these findings add their weight to the thesis that this disease belongs within the allergic category. Rather indirect evidence against this is the

lack of response to hypodermic epinephrine administered in the acute episode (cases 1, 2 and 5).

A more serious argument against the allergic postulate is the difficulty in discovering any causative allergic factor. It would be tempting to conclude from some of the observations already noted that all cases of benign paroxysmal peritonitis are due simply to food allergy. Such an assumption is not warranted by the available experience. In three of the author's series careful investigation has not revealed the causative food allergen. In the remaining two cases less complete study has likewise been negative. The delayed form of food allergy with negative skin tests is a notoriously complex problem. In some instances, despite carefully kept food diaries and stringent adherence to trial diets, the offending foods may escape detection. However, efforts along these lines must be continued as food allergy is at present the only available clue to possible cure of these cases.

It is possible that some other allergic mechanism operates in those cases without evident food hypersensitiveness. Bacterial sensitization, whether to upper respiratory or gastrointestinal flora, is a rather remote possibility. There is no convincing evidence, either from the clinical or laboratory point of view, to support this theory. If such bacterial vascular sensitization were postulated it would be of a different order from that possibly active in acute lupus erythematosus disseminatus.[27] Nor would it be related to the type of vascular allergy which is characterized by marked blood and tissue eosinophilia and often terminates in periarteritis nodosa.[28]

Thus, one may view this disease as allergic in nature but with many of the cases beyond solution by present technics. This would be analogous to what obtains in other presumably allergic disorders such as bronchial asthma or vasomotor rhinitis. Or it may be grouped with other paroxysmal, and often vascular, disturbances such as migraine, Ménière's syndrome, angioneurotic edema or the Henoch-Schoenlein form of purpura. Some cases of each of these have been shown to be allergic, although the vast majority belong at present to the category of disorders of unknown origin.

Within the past year M. T. Moore [29] has reported a case of paroxysmal abdominal pain of 31 years' duration in which an abnormal electroencephalogram was found, and the attacks prevented by means of dilantin therapy. Nothing was stated as to the presence of fever or unusual abdominal findings. In a personal communication Moore writes: "The patient . . . had a mild rise of temperature during the bouts. Insofar as the actual status of the abdomen was concerned, nothing more than increased intestinal activity was apparent." In case 2 of the author's group an entirely normal electroencephalogram is reported by Dr. Hans Strauss. The clinical manifestations of the present series appear to offer distinct differences from Moore's case but further observations along these lines may be worthwhile.

Diagnosis and Treatment

This syndrome presents a double problem in diagnosis. The first is that of the acute episode when first observed; the second that of the disease in its entirety. The correct diagnosis of the acute paroxysm, particularly when encountered early in the course of the illness, may be extremely difficult. As already noted the attack may closely simulate acute appendicitis and emergency operation be advised (see cases 1 and 5). Acute cholecystitis may also be suspected although the youth of the patient is likely to argue against this diagnosis.

Certain characteristics of the acute attack of benign paroxysmal peritonitis differ from the more usual surgical inflammations of the abdomen. Any of the following findings should place the physician on his guard:

1. An unusual degree of abdominal tenderness, both direct and rebound, beyond what would be expected with a surgical lesion of equivalent duration.
2. A considerable febrile reaction, 103° F. or more, unusual for a surgical inflammation in an early stage. If the patient is observed for 24 hours the temperature drops strikingly, often to normal.
3. Skin lesions of a vascular type may be present. Even a single urticarial wheal should be given its due clinical weight.
4. Onset with pain in either shoulder or the occurrence of a pleuritic element in the patient's pain, too early to be explained by perforation or subphrenic extension.
5. A personal or family history of allergy.

An additional point of practical importance to correct diagnosis is that neither the presence of leukocytosis and polynucleosis nor the absence of eosinophilia excludes benign paroxysmal peritonitis.

The paroxysms are often just atypical enough so that emergency operation is avoided. The patient suffers through several such episodes, all subsiding spontaneously, and he is regarded less and less as a surgical problem. Diagnostic investigations are then carried out without positive result. The diagnosis becomes increasingly obscure as all the usual causes of abdominal pain and fever are consecutively excluded. Before the disease has been of too long duration acute mesenteric adenitis, abdominal Hodgkin's disease, hepatic abscess and undulant fever will be considered. Persistently negative findings and the further course of the disease finally rule out all such possibilities. In women the condition must be distinguished from the syndrome of ruptured Graafian follicle or corpus luteum cyst of the ovary, with peritoneal irritation. The absence of any evidence of internal bleeding and the frequent recurrence of attacks over many years ultimately excludes these causes also.

Sooner or later it is recognized that the syndrome falls into no accepted category. Psychiatric causes will be considered and even malingering will be thought of. However, the obviously genuine clinical pattern of the disease, together with the fever and leukocytosis, excludes the latter and makes

the former unlikely. If cases occur where the fever is slight or on occasion absent the patient may be permanently classified as "neurotic," often with no further effort made to understand the origins of his illness.

Exploratory laparotomy is likely to be recommended when all other diagnostic measures have failed. As this disease becomes more widely recognized, operation for this purpose will become unnecessary. However, in the individual case where abdominal exploration is deemed wise it is urged that it be done during an acute attack rather than in a free interval. The underlying pathologic reaction of the disease can be observed, or other lesions such as an internal hernia with incomplete obstruction, or torsion of an internal cyst or appendix epiploica, rare though they be, will be discernible only at this stage. An interval operation is likely to be totally unrevealing.

Operation should not be performed until the patient has had the benefit of a complete allergic study. Intradermal testing though of possible value forms the least part of this investigation. Painstaking and prolonged experimentation with trial and addition diets together with the use of a food diary comprise the most valuable methods. The allergic approach, being at present the only fruitful one, should be pushed to the utmost.

From the standpoint of medicinal therapy various pharmacologic agents should be tried. Adrenalin, gynergen, atropine sulfate, ephedrine, and nicotinic acid should all be used during the acute attack in an effort to abort it. Continuous treatment with several of these drugs may also be attempted in the hope that attacks may be prevented. Experience with both forms of therapy has thus far been disappointing.

Summary

Five cases are presented illustrating an unusual syndrome consisting of paroxysms of intense abdominal pain with fever as high as 105° F. Severe prostration, marked signs of peritoneal irritation, as well as nausea and vomiting, are invariable accompaniments. Urticaria and chest pain of a pleuritic type may occur. Onset of the disease is characteristically in early life and the attacks recur frequently over many years. The patients' general health remains unimpaired. The nature of this bizarre disorder is discussed together with its probable relationship to allergy. Suggestions are offered as to diagnosis and treatment.

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TISSUE CALCIFICATION AND RENAL FAILURE PRODUCED BY MASSIVE DOSE VITAMIN D THERAPY OF ARTHRITIS *

By T. S. Danowski, M.D., A. W. Winkler, F.A.C.P., and J. P. Peters, M.D., *New Haven, Connecticut*

Massive doses of vitamin D have been used in the treatment of arthritis during the past decade.[1, 2] Symptoms and physical disabilities of some patients have apparently improved on this régime. The clinical reports have usually implied that the toxic effects of these large doses are insignificant.[3, 4, 5, 6, 7] In this report two cases of renal damage secondary to prolonged therapy with vitamin D are described. In one of these extensive calcification of soft tissues was readily demonstrable.

Case Reports

Case 1 (E. S.) This English housewife was first admitted to New Haven Hospital in 1932 at the age of 47 for study of a painful, deforming arthritis of the extremities which had begun 18 years earlier. Despite tonsillectomy, two antrotomies, a submucous resection, dental extractions, abdominal laparotomy, foreign protein injections, and vaccine therapy the disease had been progressive from its onset. The patient had, however, been well otherwise.

At the time of this admission and during five subsequent admissions in the next two years the abnormal physical findings were limited to the extremities. The soft tissues of the hands and feet were atrophied; deformity and markedly restricted range of motion of the large and small joints of all extremities, typical of rheumatoid arthritis, were present. Partial ankylosis of the hip and shoulder joints was evident. The patient also had chronic pansinusitis and deafness of the conduction type.

Laboratory studies at this time were entirely within normal limits (table 1a). Roentgenographic examination of the right wrist and hand (figure 1) and of the hips revealed narrowing of the joint spaces with thinning of the adjacent bone. There was no generalized osteoporosis.

The patient did not improve significantly under physiotherapy, nor following courses of glycine and of dinitrophenol. She was not seen again for eight years. During this period she received local treatment for the sinusitis. The arthritis persisted and markedly restricted the patient's activity. From 1936 to 1942 she took 150,000 to 200,000 units of vitamin D daily as therapy of the arthritis. Attempts to increase the dosage to 450,000 during a two month period in 1941 produced gastrointestinal distress. In May 1942 a swelling appeared near the left wrist and the patient discontinued the intake of vitamin.

She returned in November 1942 for the first of a series of four admissions for treatment of localized fluctuant swellings at the left wrist and the right ankle. The physical findings, except for further loss of hearing, were otherwise unchanged. The patient did not have hypertension.

Repetition of laboratory studies revealed anemia and renal insufficiency (table 1b). Azotemia, low specific gravity of urine, two plus albuminuria, casts, and a decreased

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From the Department of Internal Medicine, Yale University School of Medicine.

TABLE I

	Blood			Serum				Urine			
	Erythrocytes, per cu. mm.	Hgb., gm.	NPN, mg. per cent	Albumin, gm. per cent	Globulin, gm. per cent	Ca, mg. per cent	P, mg. per cent	Alb.	Casts	Spec. Gravity	PSP Excretion per cent
Patient: E. S.											
A. Before vitamin D											
1932	4.6	13	20	4.24	2.85	10.20	3.81	0	0	1.028	
1934	4.8	14	34	3.93	3.26	10.86	3.65	0	0	1.023	
B. After 6 years on vitamin D											
November 1942	2.9	8.5	67	3.69	2.06	15.37	4.53	++	+	1.013	15
C. After cessation of vitamin D											
April 1943	3.7	10.5	53	4.02	1.98	13.81	4.45	+	+	1.013	30
December 1943	4.2	12.5	46	3.48	2.91	11.77	3.60	+	0	1.013	30
January 1945	4.2	10.5	50	4.26	2.76	9.24	2.45	0	0	1.009	35
Patient: H. W.											
D. After 7 months on vitamin D											
October 1944	3.0	9.0	55	4.52	2.41	14.47	5.23	++	+	1.005	20
E. After cessation of vitamin D											
November 1944	3.6	9.6	41	4.57	1.71	11.99	3.30	+	+	1.014	27
January 1945	4.1	11.5	47	4.22	2.11	9.40	3.24	+	+	1.015	35

excretion of phenolsulphonphthalein dye were all present. In addition, the concentrations of calcium and phosphorus in serum had become elevated, in contrast to their previously normal values. Roentgenograms showed decalcification of all bones except the skull, narrowing or destruction of joint spaces, and extensive calcific deposits in the soft tissues of the hands, wrists (figure 2), and right ankle. There was no calcification seen in the abdominal organs.

The localized swellings were incised, yielding red gelatinous or white chalk-like material containing calcium. These lesions healed by granulation only after months of persistent discharge.

One and one half years after cessation of vitamin D therapy the concentration of serum calcium had fallen to 11.77 milligrams per cent, and the serum phosphorus was normal. The albuminuria had diminished to one plus. Two and one half years later the swellings had not recurred and the patient's hearing had improved distinctly. The serum calcium and phosphorus values had returned to normal. The non-protein nitrogen of the blood was still elevated at 50 milligrams per cent, but the urine was free of albumin and casts (table 1c).

Repeat roentgenograms at this time revealed a striking decrease or complete disappearance of the calcium deposits in the soft tissues of the hands, wrists (figure 3), and of the right ankle. In addition complete destruction and absorption of some of the bones of the wrists were evident, together with concentric decrease in the head of the right femur and movement of the right acetabular surface upward.

Case 2 (H. W.). This 56 year old Irish widow was admitted initially with intermittent abdominal cramps, nausea, and vomiting of three months' duration associated

FIG. 1. Roentgenogram of patient E. S. in 1932 showing atrophic arthritis of the right hand and wrist of 18 years' duration.

FIG. 2. Roentgenograms of hands and wrists of patient E. S. in 1942 showing destruction of joint spaces, osteoporosis of the adjacent bone, and calcification in the periarticular tissues after six years of therapy with vitamin D.

with an 11 pound weight loss. The past history included scarlet fever at the age of two, a stay of 18 months in a sanatorium at the age of 18 for treatment of pulmonary tuberculosis, irradiation therapy of uterine fibromata at the age of 34, and pain in the right hip and leg following a minor fall at the age of 44. During the 10 years preceding admission the patient had experienced intermittent pain in the joints of all extremities without any objective change noted. In January 1944 the patient was advised by her physician to take vitamin D as treatment for the arthritic pain. The initial daily dose of 50,000 units was increased in the course of the next eight weeks to 500,000 units and maintained at that level for five months, ending two months before admission. The patient experienced nausea and vomiting for about 24 hours following each increase in dosage. During this seven month period she took at least one quart of milk daily.

FIG. 3. Repeat roentgenograms of patient E. S. two and one half years after cessation of vitamin D administration showing partial or complete resorption of calcium deposited in the soft tissues. Striking destruction or complete disappearance of the bones of the wrists is evident, most marked on the left.

Review of systems indicated that within the year preceding admission the patient had developed a slight cough, exertional dyspnea, and orthopnea, and that the blood pressure had been found to be high.

In the course of this and two subsequent admissions to the hospital the blood pressure ranged from 240 mm. Hg systolic and 120 mm. diastolic to 190 mm. systolic and 100 mm. diastolic. Positive findings on physical examination included the presence of resolving hemorrhages in the left fundus, cardiac enlargement, a precordial systolic murmur, edema of the ankles, and Heberden's nodes.

Laboratory studies revealed hypochromic anemia, an elevated blood non-protein nitrogen content, urine of low specific gravity, and poor excretion of phenolsulphonphthalein dye (table 1d). The concentration of serum bicarbonate was slightly reduced. A distinct hypercalcemia existed together with an increased concentration of serum phosphorus. Roentgenographic studies showed fibrotic pulmonary tuberculosis

of the right upper lobe, cardiac enlargement, diverticulosis of the descending colon, and a compression fracture of the twelfth dorsal vertebra. The skull was osteoporotic; proliferations of bone were seen at the knee and hip joints, and on the vertebral bodies, of the type associated with hypertrophic osteoarthritis. There was no metastatic calcification. The electrocardiogram was characterized by low T-waves in limb Leads I and II, and slight left axis shift. Urine cultures were negative.

With digitalization and rest in bed the patient lost 4.3 kilograms of edema fluid. Repeated serum calcium and phosphorus determinations showed a gradual return to normal values during the next 12 weeks. The hypertension and the renal failure persisted (table 1e).†

Discussion

These two cases indicate clearly that patients treated for a prolonged period with massive doses of vitamin D may develop calcification of soft tissues and renal damage. Renal complications may be less uncommon than the paucity of such clinical reports would indicate, since the azotemia and minimal albuminuria which characterize them might be overlooked or ascribed to other causes.

Vitamin D in large doses provokes a hypercalcemia, and increases the calcium content of the soft tissues, particularly of the kidney.[8] The hypercalcemia favors metastatic calcification. This may be facilitated by local tissue injury already present, or produced by the vitamin D itself.[9] Renal calcification affords, therefore, a satisfactory explanation of the renal damage observed in these two patients, even though the calcium deposited in the kidneys was too low in concentration to be demonstrated in roentgenograms. Similar cases have been reported by Thatcher,[10, 11] and by Tumulty and Howard,[12] following Putschar's description[13] of calcium deposits in the kidneys of an infant who died with hypercalcemia produced by a preparation of irradiated ergosterol.

This impairment of renal function by vitamin D is to a considerable extent reversible. The kidney function in the two young patients reported by Tumulty and Howard improved following cessation of vitamin D therapy, but poor concentrating ability persisted as a residuum of the renal injury produced by irradiated ergosterol.[12] In the two cases reported in the present paper interruption of vitamin D after months and years of therapy was followed by a return of renal function toward normal without complete resolution. It is of interest in this connection to note that the subcutaneous metastatic calcification of patient E. S. was eventually almost completely reabsorbed. Presumably, a similar decrease in calcium occurred in the kidney. The extent of the fibroblastic proliferation about the calcified areas in the kidneys probably determines the completeness with which the renal lesions may resolve. However, intrinsic renal disease independent of that produced by vitamin D injury cannot be excluded as a factor limiting the degree of recovery possible.

† (June, 1945) The blood pressure returned to normal limits in March, 1945.

Patient H. W. received a proprietary form of vitamin D prepared by the Whittier process of heat vaporization and subsequent electrical activation of ergosterol. This product has been reported less toxic than the vitamin D formed by ultraviolet irradiation or ergosterol.[3, 4, 5, 6, 7] However, even in these reports patients treated with the electrically activated product at times developed hypercalcemia, anorexia, nausea, and vomiting. Polyuria and nocturia were also noted occasionally. These symptoms, which disappeared as the dosage was decreased, are identical with the early phases of intoxication with irradiated ergosterol.[12, 14] It would appear, therefore, that vitamin D prepared by either method may produce the same toxic effects. This is confirmed by the experience with the two patients described in this report.

The extensive destruction of bone evident in the wrists and right hip of patient E. S. is an anomalous development in the natural course of atrophic arthritis. It suggests that the extensive intake of vitamin D together with a low intake of calcium and phosphorus produced disruption of the histology of the bone of the type reported in rats,[15] with subsequent absorption of the injured bone. During the first five of the six years of therapy this patient did not drink milk nor did she receive supplementary calcium. In the last year she took one or two glasses of milk daily during a period of one month.

No clear principle has been formulated for a rational use of vitamin D in arthritis. Its introduction followed the chance finding that patients receiving this vitamin for allergic conditions experienced a coincident improvement in arthritis.[1, 2] It has been shown experimentally in rats that vitamin D may produce either an increase or a decrease in the bone ash, depending upon the dose.[16] This offers, in theory, a logical approach to therapy through attempts either to correct the osteoporosis, or to remove abnormal proliferations of bone. Clinically, however, improvement in arthritis reported during administration of vitamin D is not correlated with any consistent alteration in the density of the skeleton or of exostoses.[3, 4] In serial roentgenograms the osteoporosis may increase, decrease, or remain unchanged. There is also no evidence that improvement is related to the development of hypercalcemia. It seems clear, therefore, that the favorable effects of vitamin D reported in arthritis are unrelated to the metabolism of calcium and phosphorus. This is not surprising in view of the repeated failure to demonstrate any definite abnormality in the calcium and phosphorus balance of patients with arthritis.[17, 18, 19]

As a practical matter, it is evident that the therapy of arthritis with vitamin D demands careful supervision. The patient should never be permitted to continue treatment on his own initiative. Frequent determinations of the serum calcium with prompt reduction of dosage if hypercalcemia develops are essential. Repeated examinations of the urine and blood pressure must be made if renal complications are to be avoided.

The experience with patient H. W. stresses the necessity for careful questioning about previous intake of vitamin D. Because of the hyper-

calcemia she was at first suspected of hyperparathyroidism. Only through detailed inquiry was the history of vitamin D therapy obtained. This search should be made in all cases of unexplained hypercalcemia, lest the patient be subjected to an unnecessary exploration for an adenoma of the parathyroid gland.

SUMMARY

1. Two cases are reported of hypercalcemia and of renal failure produced by massive dose therapy of arthritis with vitamin D.

2. Administration of vitamin D to patients with arthritis in amounts sufficient to produce hypercalcemia is unjustified.

3. Hypervitaminosis D is to be considered in the differential diagnosis of hypercalcemia.

The authors are indebted to Dr. Hugh M. Wilson, Professor of Radiology, Yale University School of Medicine, and Radiologist-in-Chief of the New Haven Hospital, for interpretations of the roentgenograms.

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THE SYNDROME OF PSOAS MYOSITIS AND FIBROSITIS; ITS MANIFESTATIONS AND ITS SIGNIFICANCE IN THE DIFFERENTIAL DIAGNOSIS OF LOWER ABDOMINAL PAIN *

By JAMES A. GREENE, M.D., F.A.C.P., *Houston, Texas*

PAIN and tenderness in the psoas muscle which is probably attributable to myositis or fibrositis has been known for many years, but its importance in the differential diagnosis of lower abdominal disease has not been emphasized sufficiently. During the past few years I have observed this syndrome in over 50 cases varying in age from 16 to 60 years. It has been mistaken for other diseases in most instances. In 25 of the 50 cases abdominal operations have been performed alone or in conjunction with perineal repair because of mistaken diagnosis. In addition, many of these patients have become extremely anxious regarding their condition because they have consulted several physicians without a diagnosis being established. In some instances the diagnosis of psychoneurosis has been erroneously attached to the patient. It is for these reasons that I wish to call attention to this syndrome, to emphasize its frequency and importance in the differential diagnosis of lower abdominal pain, and discuss its manifestations.

The more common subjective manifestation of this syndrome is pain in the lower quadrants of the abdomen. It may be unilateral or bilateral and is usually dull and aching in character. It may persist for days, weeks, months or even years, but acute exacerbations of sharp pain occur. With careful inquiry it will be noted that the pain is increased with activity which increases the use of these muscles and it is ameliorated by cessation of such activity, although it usually does not entirely disappear. The onset is insidious but may be sudden. Exacerbations and remissions with complete disappearance of symptoms are common, but in some instances it has persisted for years. Sacroiliac syndrome and fibrositis of other muscles are common accompaniments.

The only definite objective manifestation is tenderness over the psoas muscle. This tenderness is increased when the muscle is contracted or stretched and, as a rule, extends from the origin of the muscle along its entire course to the tendon and to its insertion into the femur. Both psoas muscles are frequently involved, but one side is usually the more severe.

The etiology cannot be ascertained in many instances. On the other hand, trauma, defects in body posture, or acute infections appear to be exciting causes. In others the syndrome follows pregnancy or is associated with the sacroiliac syndrome.

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From the Department of Internal Medicine, Baylor University, College of Medicine, Houston, Texas.

Other conditions usually accompany the psoas fibrositis. The more common of these are sacroiliac syndrome, fibrositis of other muscles, or anxiety manifestations. Only 10 of the 50 cases exhibited manifestations of psoas fibrositis alone. Cases 1, 2 and 3 are typical illustrations of this variety. In cases 1 and 2 the pain was unilateral, whereas in case 3 it was bilateral. Trauma was apparently the etiology in case 1, but no causative factor was ascertained in the other two cases.

Those associated with sacroiliac syndrome may develop following a sacroiliac strain, following pregnancy or from no apparent cause. In such instances the relative prominence of the subjective manifestations of the two syndromes varies. In some the sacroiliac predominates, in others the psoas fibrositis, and in others both are of equal intensity as illustrated by cases 4 and 5.

If fibrositis of other muscles is present the predominating manifestations may be those arising from the psoas muscle or those arising from other muscles. The muscles of the thoracic wall, shoulder and cervical region are the more common ones involved in association with the psoas syndrome. In most instances the pains in the lower abdomen and those in the other muscles are considered by the patient to be separate and distinct diseases. Case 6 is a typical illustration.

The manifestations of anxiety may dominate the picture if the psoas syndrome occurs in a "high-strung" individual, if it is of long standing, if the diagnosis has not been established, or if an erroneous diagnosis has been made. This is typically illustrated by case 7.

In some instances attacks recur for years and various therapeutic measures have been employed without benefit. The patient may have been subjected to unnecessary major surgical procedures as was the situation in case 8.

In the differential diagnosis lesions of the appendix, small bowel, colon, urinary tract, uterus, Fallopian tubes, ovaries and vertebral column must be excluded. Disease of any of these may irritate the psoas muscle and produce the manifestations of fibrositis of this muscle. Appendicitis is extremely difficult to exclude in many instances, but irritation from this cause is usually localized to the body of the muscle and does not extend along the entire course of the muscle and tendon to its insertion into the femur as is usually the case with fibrositis. Involvement of the other psoas major muscle is additional evidence in favor of fibrositis and is against localized irritation due to disease of a neighboring organ. The absence of fever and leukocytosis is against, but does not exclude appendicitis. Diseases of the urinary tract, ovaries, Fallopian tubes, uterus and vertebrae are not likely to be confused with the psoas syndrome if all are considered and an adequate examination is made. The diagnosis of irritability of the colon has been made in many of the observed cases. The tenderness in the cecal and sigmoid regions is suggestive of disease of the colon, but if the sigmoid is moved

to one side one can easily ascertain that the tenderness is in the muscle. The colon may be irritable in some instances, but in most cases of psoas fibrositis it is not.

The treatment employed in most cases has been rest of the affected muscles and salicylates in 5 to 15 grain doses three to four times daily. The response to therapy has been excellent in most instances. In cases with an associated sacroiliac syndrome the additional therapeutic measure of application of adhesive tape to the lower back or a sacroiliac belt may be necessary. Postural defects must be corrected if present and activities involving use of the psoas muscles should be omitted. The anxiety manifestations, if present, are easily controlled and eliminated, as a rule, when the condition is explained to the patient and when the response to the treatment is demonstrated. The psoas fibrositis has failed to respond to the above treatment in only two cases. In one the muscle was injected with novocaine without benefit, but later responded to the administration of neocincophen. The other patient, case 6, became convinced that the pains were arising in the muscles and preferred not to have the muscle injected with novocaine or to take neocincophen. The accompanying fibrositis in her trapezius muscle, however, responded to the injection of novocaine.

Case Reports

Case 1. A white girl, aged 17 years, first entered the hospital in December 1933 for pain in the right lower quadrant of the abdomen of approximately one month's duration. She had fallen across a frozen corn-row striking the right lower abdomen and the resulting pain was fairly severe but did not incapacitate her. The following morning the pain had disappeared but soreness persisted. Approximately three weeks later she had forgotten about the fall and consulted her local physician who thought that she had appendicitis. After she spent a few days in bed the pain decreased but did not disappear. She was admitted to the hospital and an appendectomy was performed without relief of the pain. A diagnosis of irritability of the colon was made and she was treated for several months without improvement. She returned to the hospital several times during the next three years and was examined by members of the staff of the medical, surgical, gynecological, urological, orthopedic, neurologic, and psychiatric departments without any causative factor being discovered or effective treatment instituted. I had seen the patient upon several occasions before the possibility of psoas fibrositis was considered. The right psoas muscle was extremely tender and when the muscle was contracted or stretched pressure over the muscle was unbearable. There was no evidence of fibrositis elsewhere and the left psoas muscle was not tender. The pain was controlled by salicylate therapy.

Case 2. A white male, aged 35 years, consulted me on July 20, 1937, for pain in the left lower abdomen of six weeks' duration. He had been well until the previous June when he had an attack of diarrhea of three days' duration. There was no accompanying fever, chills or melena. A few days later he noted a pain in the left lower abdomen and consulted his local physician. Stool examinations for occult and gross blood and roentgenograms of the colon were negative. The usual regimen for irritability of the colon was followed very rigidly for six weeks without relief. The only abnormal physical finding was tenderness in the lower left abdomen. Proctoscopic examination, repeated examinations of stools for blood and pathogenic organisms and roentgenograms of the colon were negative. Several modifications of the

above regimen were tried for four months without relief. Finally the possibility of psoas fibrositis was considered and the left psoas muscle was only slightly tender until it was contracted or stretched and then it became extreme. The pain disappeared following salicylate therapy.

Case 3. A white single woman, aged 52 years, consulted me November 12, 1941, for pain in both lower quadrants of the abdomen of four to six months' duration. She had had an appendectomy many years before, but otherwise had been well. She was unable to state the exact time of onset of the pain, but the pain in the right side was the more severe. It was described as dull, aching in character, varied in intensity from barely perceptible to very annoying. She worked in a small postoffice and the handling of packages caused her to stoop and squat a great deal. The pain was almost invariably improved on the days she did not work. Her local physician prescribed the usual regimen for irritability of the colon which gave her no improvement. The only objective manifestation was tenderness over both psoas muscles which was greatly increased by contracting or stretching the muscles. The pain disappeared with salicylate therapy.

Case 4. A white married woman, aged 26 years, consulted me September 10, 1941, for pains in both lower quadrants of the abdomen and in the lower back of three months' duration. She had consulted three physicians and was informed by one that she had disease of her pelvic organs; by another that she had appendicitis, and by the third that she had irritability of the colon. The only objective manifestations were tenderness over both psoas muscles and both sacroiliac regions. The pains were relieved by application of adhesive tape to lower back and salicylate therapy.

Case 5. A white married woman, aged 24 years, consulted me April 16, 1942, for pain in both lower quadrants of the abdomen of two years' duration. She had had two normal full-term pregnancies and had noticed the pain very soon after the last one. The pain was variable, but had annoyed her most of the time for the two years. A perineal repair and a suspension of the uterus had been performed without relief. The appendix was removed also without amelioration of the pain. The only objective manifestations were tenderness over the psoas muscles and sacroiliac regions. The pain disappeared with salicylate therapy.

Case 6. A white married woman, nurse, aged 35 years, consulted me February 2, 1942 for pain in right lower abdomen of four years' duration and pains in the breasts of two years' duration. She had been examined thoroughly by several excellent physicians and in two widely known clinics without a definite diagnosis being established. She had become greatly concerned and had become convinced that she had some serious disease in the abdomen and in the breasts. These pains increased and decreased, but never completely subsided. Similar pains had been noted in the shoulders, neck and arms, but they would entirely disappear. The physical examination showed that the intercostal muscles, trapezius and psoas muscles were tender and pressure over the psoas muscles reproduced the pain in the lower abdomen. The pains were ameliorated but did not disappear with salicylate therapy. The pain in the left trapezius disappeared following novocaine injection.

Case 7. A white widowed woman, aged 52 years, consulted me April 7, 1942, for nocturnal sweating, palpitation of the heart, loss of weight, hot flashes, nervousness and pains in the lower abdomen. She had enjoyed good health until three years previously. At this time she frequently assisted the nurse in lifting and turning her husband during his final illness and began to note pains in the lower abdomen. These pains subsided after her husband's death but reappeared at intervals. She consulted several physicians and had her appendix removed without benefit. She had been advised to have a hysterectomy, and had followed a regimen for irritability of the colon for over a year without relief. These pains caused her great anxiety and she feared that she had a cancer or tumor. As the anxiety increased those symptoms be-

came the predominant ones. During the previous three months the pains were greatly increased by walking and were ameliorated by resting. She was unable to walk over three city blocks without the pains becoming very annoying. The only objective manifestations were emaciation and tenderness over the psoas muscles which reproduced the lower abdominal pain. The abdominal pains were relieved by salicylate therapy.

Case 8. A white married woman, aged 65 years, entered the hospital complaining of pain in the right mid and lower abdomen of several months' duration. The attacks of pain began about 15 to 18 years previously, lasted several months each time, and recurred at two to four year intervals. During her initial attack the appendix was removed and during a subsequent attack the uterus and ovaries were removed. These organs showed no definite disease and she obtained no relief from the operations. Later some abnormality of the right kidney was discovered and the right kidney was removed without relief of the pain. During the last attack a stone was found in the gall-bladder and a cholecystectomy was performed without influencing the pain. The pain apparently subsided spontaneously during each previous attack. It was greatly aggravated in each attack by standing or walking for only a few minutes. The right psoas muscle was very tender and pressure over it reproduced the pain. No other abnormality could be ascertained. This pain subsided with salicylate therapy.

Summary

The manifestations of the syndrome of myositis and fibrositis of the psoas muscles are presented. The frequency and importance of this syndrome in the differential diagnosis of lower abdominal pain are emphasized. The reports of eight cases are included to illustrate the variations the syndrome may assume. The therapeutic measures employed and the results obtained are discussed.

AIDS IN PHYSICAL DIAGNOSIS: SIGNS OVER THE LOWER LEFT LUNG CAUSED CHIEFLY BY CARDIAC ENLARGEMENT *

By Earle M. Chapman, M.D., F.A.C.P., and Robin G. Anderson, M.D.,
Boston, Massachusetts

In 1896 William Ewart, physician to St. George's Hospital in London, described [1] what he termed his crucial signs of pericardial effusion. Clinicians have long appreciated Ewart's signs † and in 1918 Dr. H. A. Christian [2] reported their presence in 73 per cent of his cases of acute fibrinous pericarditis. L. A. Connor in the first issue of the American Heart Journal likewise called attention to these signs.[3] We have observed a somewhat similar group of physical signs over the left lower lung but in no case was there evidence of pericarditis or pericardial effusion to explain the physical changes. Likewise we have observed physicians in diagnostic error because of a misinterpretation of these signs.

It is our purpose to call attention to these signs that have not been described adequately in the medical literature and clearly to distinguish them from those of Ewart. It seems that all types of cardiac enlargement may cause these several signs over the left lower lobe and that they are not peculiar to any particular heart shape. In our illustrative cases it will be noted that these signs were associated with general enlargement of the heart; the enlargement of the left ventricle seen especially in hypertensive disease; the enlargement of the auricles and ventricles seen in severe rheumatic heart disease with several valves involved; the enlargement of the heart chiefly in the region of the left auricle from mitral stenosis alone; and finally the rather slight enlargement of congenital type.

We believe our signs represent a compression of the left lower lobe most often caused by an enlarged heart; certainly this is a clinical syndrome that has been appreciated for years but one which curiously has escaped description in recent texts and so has been a neglected fact in recent teaching. However, as Dr. John Homans, in delivering the dedicatory address at the Yale Medical Library, said: "Discoveries are perennially being made, affirmed, forgotten, lost, found again and finally placed on record and universally accepted."

Vaquez [4] referred to the use of dorsal percussion in measuring heart size and properly accredited Piorry [5] with having introduced this technic in 1866. In this era before the clinical use of the roentgen-ray Barie [6] reviewed the previous work of Pirogoff, Luschka and Poirier who demonstrated on cadavers that the normal left auricle lies just to the left of the sixth to

* Received for publication September 11, 1944.

† We can find no authority of Ewart's sign accredited with the same in Dorland's dictionary.

seventh dorsal vertebrae and that with a forceful percussion note one might elicit a 3 by 7 cm. oval area of dullness in this area that outlined the left auricle. This rather precise and difficult technic was probably accepted by very few clinicians and we wish to add that nothing was said about the other important signs of tactile and vocal fremitus and the auscultatory changes. White [7] also mentions very infrequent changes at the left base occurring especially in rheumatic disease with a large left auricle but nowhere can we discover that this subject has been reëvaluated since the clinical application of the roentgen-ray.

The chief sign that we have observed in this topographical area of the left lower lobe has been an area of *dullness* just below the angle of the left scapula. However, this finding is not constant in cardiac hypertrophy nor

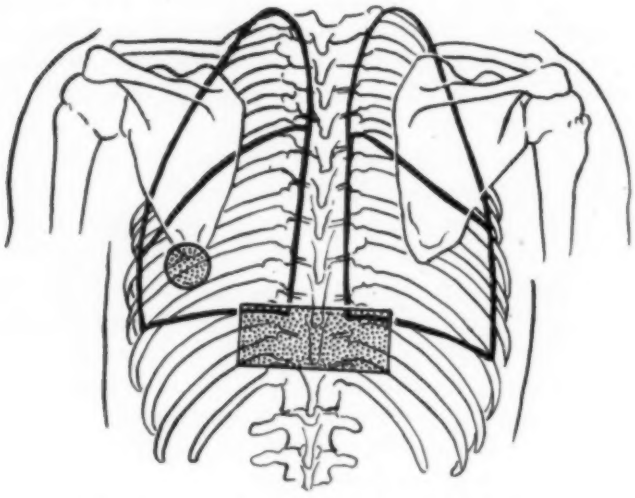

FIG. 1. Ewart's signs of pericardial effusion.

has it always been present when other abnormal signs were discovered. In some instances the dull note could be elicited only by a very heavy percussion which suggested that the shorter and higher pitched note was due to the sound waves penetrating normal lung and being absorbed or reflected by the enlarged cardiac mass. This concept we have mentioned in a previous publication.[8] The changes in *tactile fremitus* at the left base are difficult to evaluate as in the normal there is greater fremitus over the right base due to the direct anatomical position of the right descending bronchus. *Auscultatory changes* have most often been a prolonged expiration, varying from those described as bronchovesicular to bronchial; in some the breath sounds were diminished, and moist, crepitant râles were heard. The voice sounds in some were altered so as to give an increased, almost nasal sound. *With this group of changes from the normal it is plain that we are not de-*

scribing a fixed set of signs but rather indicating that variable changes from the normal occur with surprising frequency over the left base. In fact, we are reminded of Richard Cabot's remark that the pulmonic area is the region of "auscultatory romance" for cardiac murmurs, and we are tempted to add that the region of the left base is the region of "romance" for pulmonary findings.

The explanation for these changes encountered over the left lower lobe has not always been clear, but with anatomic and physiologic facts in correlation we have sought an adequate explanation. Normal variations in size, position and degree of patency of the left lower lobe bronchus may greatly affect physical signs over this lobe; the evidence of Klopstock [9] that the pulmonary blood flow is greatest throughout the left lower lobe also suggests

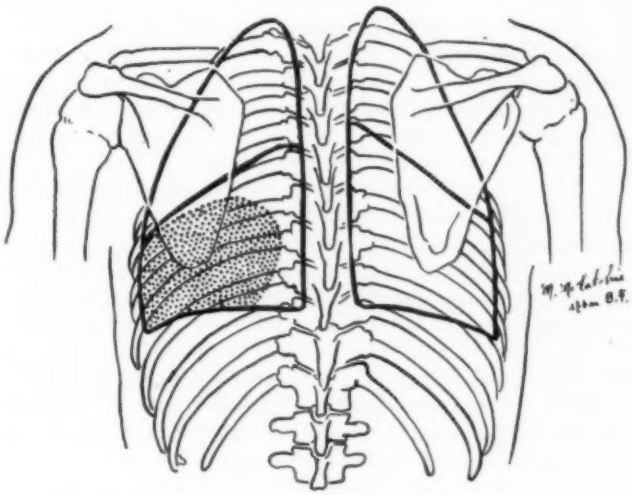

FIG. 2. Our signs over left lobe.

physical changes in this area; from his observations he postulated that pulmonary emboli (bacterial or coagulated blood) usually strike this lobe first and the clinical evidence of Allen, Linton and Donaldson [10] indicates that 70 per cent of pulmonary emboli slither into the left lower lobe. In addition to these facts it is known from the surgical experience of Churchill [11] that the incidence of bronchiectasis is greatest in the left lower lobe; this point is also stressed in that excellent study of Olgivie's on "The Natural History of Bronchiectasis." [12]

In these patients in whom we have observed changes at the left base we believe we have established the fact that they did not have pulmonary infarction, bronchiectasis, collapse of the lung, pneumonitis, congestion, pleural effusion, an elevated diaphragm or a tumor mass that caused these signs. The ordinary chest films in all cases were scrutinized carefully with these diagnoses in mind and in most cases it will be noted that oblique and lateral films

of the left lung were also obtained. Certainly none of them had pericardial effusion. And in conclusion we believe that in those patients with a markedly enlarged heart, especially those with rheumatic disease in whom the left auricle was enlarged, the abnormal physical signs at the left base are a result of this mass plus the factor of pulmonary compression.

In confirmation we wish to submit these case examples from patients observed in the Massachusetts General Hospital.

Key { P = Percussion; TF = Tactile fremitus; SV = Spoken voice sounds; WV = Whispered voice sounds; BS = Breath sounds }

1. *Unit No. 314382.* A 50 year old housewife with essential hypertension ranging from 210 mm. Hg systolic and 120 mm. diastolic to 236 mm. systolic and 136 mm. diastolic was examined on August 7, 1941 and showed P normal, TF normal, SV normal, BS bronchial, 0 râles.

Chest roentgen-rays on August 14, 1941 reported the heart enlarged in the region of the left ventricle; measurements 12.8 cm. at apex, 22.1 cm. transverse chest. Views in the oblique and lateral view showed no lung disease.

2. *Unit No. 318256.* A 43 year old male with gout, chronic Bright's disease and hypertension, 215 mm. Hg systolic and 145 mm. diastolic; on September 25, 1941 physical examination of the chest showed P normal, TF increased, SV increased, BS bronchial.

Chest roentgen-rays that day confirmed the cardiac enlargement, especially to the left; measurements 17.8 cm. at apex, 32 cm. transverse chest. Left lung clear in oblique and lateral films.

3. *Unit No. 117395.* A 38 year old man with nephrolithiasis and pyelonephritis; the left kidney had been removed. His blood pressure averaged 134 mm. Hg systolic and 86 mm. diastolic. On physical examination on July 31, 1941 the chest showed P slight dullness, TF increased, SV normal, BS normal, 0 râles.

Chest roentgen-rays on July 11, 1941: The lung fields were clear, diaphragm normal in position and the heart was only slightly enlarged in the region of the left ventricle. The aorta was tortuous; measurements 14 cm. at apex, 28.9 cm. transverse chest.

4. *Unit No. 74656.* A 50 year old housewife with hypertensive heart disease and thyrotoxicosis from a large goiter partially substernal. Blood pressure was 170 mm. Hg systolic and 90 mm. diastolic. Physical examination of the chest on August 21, 1941 showed P dullness, TF diminished, BS prolonged expiration, fine râles, heart sounds heard.

On June 26, 1941 chest roentgen-rays showed a substernal thyroid with trachea slightly to the left and the heart enlarged in the region of the left ventricle; measurements 12.7 cm. at apex, 24 cm. transverse chest. The lungs were clear. The substernal goiter was removed on August 9, 1941 and the patient made an uneventful recovery. When examined again on September 17, 1941 the signs at the left base were unchanged.

5. *Unit No. 436069.* A 50 year old Swedish-American laborer with arteriosclerotic and hypertensive heart disease who entered the hospital in congestive heart failure. After loss of edema and the signs of active failure the physical examination showed on March 4, 1944, P dullness, TF dim, BS slightly prolonged expiration, 0 râles.

Roentgen-rays of chest on March 9, 1944 showed the left lung clear in the anteroposterior and oblique views. The heart was generally enlarged, especially in the region of the left ventricle. The heart measured 18 cm. at the apex and transthoracic measure was 31 cm.

6. *Unit No. 312553.* A colored boy of 19 entered the hospital with active rheumatic fever and rheumatic carditis. The blood pressure was 120 mm. Hg systolic and 80 mm. diastolic. On physical examination it was thought that the heart was normal in size and yet the chest on August 7, 1941 showed P slight dullness, TF increased, WV increased, SV nasal, BS normal.

Chest roentgen-rays on July 29, 1941 showed heart enlarged to the right consistent with a congenital heart lesion. The left auricle and pulmonary artery were prominent; measurements 14.4 cm. apex, 28 cm. transverse chest. The lung fields were clear, even in the oblique view.

7. *Unit No. 312150.* A 64 year old woman thought to have both hypertensive and rheumatic heart disease with only a single valve involved, mitral stenosis. Blood pressure 214 mm. Hg systolic and 90 mm. diastolic. Examination on July 27, 1941 showed P slight dullness, TF normal, SV normal, BS increased expiration, 0 râles.

The chest roentgen-ray revealed only slight rounding of the left ventricle, and the left lung even in lateral view was clear.

8. *Unit No. 343523.* A 23 year old boy with rheumatic heart disease, mitral stenosis and regurgitation, in congestive failure. Blood pressure 160 mm. Hg systolic and 60 mm. diastolic. Examination on March 5, 1942 showed P woody note, TF increased, VS increased, BS prolonged expiration, 0 râles.

The roentgen-rays of the chest anteroposterior and lateral on March 10, 1942 showed the heart enlarged both to the right and left in the region of the auricles and ventricles. Measurements were 25 cm. apex and 29.2 cm. transverse chest.

9. *Unit No. 306797.* A 44 year old housewife with rheumatoid arthritis and rheumatic heart disease with mitral stenosis. She entered the hospital with painful, swollen joints but no cardiac symptoms. Blood pressure was 100 mm. Hg systolic and 70 mm. diastolic. Examination on August 2, 1941 showed expansion equal, P dullness, TF increased, SV increased, BS prolonged expiration, few râles.

The roentgen-rays of the chest on June 20, 1941 presented the appearance of an enlarged left auricle typical of mitral stenosis. Measurements were 11.9 cm. apex, 23.1 cm. transverse chest. The oblique view showed no disease of the left lower lobe.

10. *Unit No. 128523.* A 15 year old boy entered the hospital with severe rheumatic heart disease with mitral stenosis and aortic stenosis and regurgitation. The blood pressure was 125 mm. Hg systolic and 56 mm. diastolic. Examination on August 27, 1941 showed P normal, TF increased, BS prolonged expiration, 0 râles.

The chest roentgen-rays on August 26, 1941 showed a heart markedly enlarged to both sides with involvement of both ventricles and especially the left auricle; measurements 17.5 cm. at apex, 24.7 cm. transverse chest. Oblique showed the left lower lung clear. This case is surprising in that the changes were not as distinct as the heart size would lead one to suspect.

11. *Unit No. 289436.* This 26 year old Italian man had rheumatic fever, recurrent, and a long-standing rheumatic heart with aortic regurgitation and probably mitral stenosis. Blood pressure 140 mm. Hg systolic and 40 mm. diastolic. On July 24, 1941 the chest examination disclosed P dullness, TF normal, SV nasal, BS diminished, 0 râles.

The roentgen-ray of the chest on August 9, 1941 showed an enlarged heart with enlargement in the region of the left auricle and right ventricle; measurements were 13.8 cm. at apex, 30 cm. transverse chest. The left lung appeared clear in the lateral and oblique views also.

12. *Unit No. 14837.* A 28 year old Irishman with severe rheumatic heart disease

with mitral stenosis and regurgitation, aortic stenosis and regurgitation and tricuspid regurgitation. Blood pressure 108 mm. Hg systolic and 74 mm. diastolic. P slight dullness, TF normal, SV increased, WV increased, BS bronchial, 0 râles.

Roentgen-rays of the chest on July 25, 1941 showed the heart enlarged in the region of the left auricle, and on fluoroscopy calcification of the mitral valve was seen. There was also slight enlargement of the pulmonary conus and the right side of the heart. Measurements at apex 12 cm., transverse chest 28 cm. The lateral views showed no disease in the left lower lung.

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DIAGNOSIS AND SURGICAL TREATMENT OF MENIERE'S DISEASE (HYDROPS OF LABYRINTH) *

By KENNETH M. DAY, M.D.,
Pittsburgh, Pennsylvania

IN 1861 Ménière first described the syndrome which bears his name. It is characterized by recurring attacks of vertigo accompanied by tinnitus, deafness and, sometimes, nausea and vomiting. Another term is "Ménière's symptom complex."

There are a number of conditions in which the Ménière syndrome may be present, as for example, catarrhal or suppurative middle ear disturbances, allergy, hemorrhage or thrombosis of labyrinthine vessels, toxic neurolabyrinthitis, multiple sclerosis, neurosyphilis, arteriosclerosis of the cerebral vessels and neoplasms. However, there remains a large group of cases exhibiting the syndrome that show no evidence of vascular, inflammatory or neoplastic processes involving the labyrinth, eighth nerve or its connections with the brain stem, the so-called idiopathic group. In recent years the term "Ménière's disease" has been used frequently to designate this group but, unfortunately, it has been very loosely applied both in this country and in England. This has resulted in many cases that exhibit the syndrome being erroneously diagnosed as Ménière's disease simply because they were insufficiently studied and the cause of their symptoms not determined. In 1938, Hallpike and Cairns [2] were the first to report on pathological changes in the labyrinth in two cases characteristic of this idiopathic group. Since then the temporal bones of some 15 further cases have been examined histologically, confirming their findings and apparently establishing a definite pathological entity. The labyrinth on the affected side showed a hydrops or distention of the endolymphatic system in all cases. Although the pathological process itself is now recognized, the etiology and nature of it are still unsolved. It had been suspected for years that the cause of many of these recurring labyrinthine attacks was an increased intralabyrinthine pressure or glaucoma of the labyrinth. Whether this be due to increased secretion of endolymph, a decreased resorption or a chemical imbalance has yet to be proved, but there is evidence supporting each of the three theories. Knowing the pathological process it is now possible clinically to differentiate these cases from all others showing the symptoms of vertigo, deafness and tinnitus and we believe the term "Ménière's disease" should be applied to this pathological condition and this alone.

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Before describing the symptomatology it might be well to define the term "vertigo." Patients' conceptions of vertigo or dizziness vary tremendously. It is a subjective symptom and we must rely on the patient's ability to describe his feeling. What the patient may call dizziness may prove to be a faintness, giddiness, light-headedness, blurring of vision, or a strange feeling in the head. True vertigo is always characterized by a sense of motion, whether linear or rotary, and a disorientation in space. It is objective when a patient's surroundings seem to move and subjective when the patient seems to move in relation to his surroundings. There is always an uncertainty of balance. The symptoms may be relatively mild and the patient staggers as though he were drunk or they may be more severe and the individual will actually fall. Secondary symptoms of nausea and vomiting, when present, are indicative of the acuity and severity of the vertigo.

The cardinal symptoms of Ménière's disease or hydrops of the labyrinth are paroxysmal attacks of vertigo associated with deafness and tinnitus, of varying intensity and frequency, often accompanied by nausea and vomiting. General physical examination and local otoscopic examination may be entirely negative. In the early stages of this disease, it is not uncommon for the vestibular labyrinth or cochlea to be involved separately, so that an accurate diagnosis cannot be made. However, with succeeding attacks, both parts of the labyrinth become jointly involved and a true diagnosis can be readily reached.

1. The deafness usually varies in severity from time to time and involves the entire scale. There are decreased bone conduction, diplacusis and distortion of sound. The patient hears tones at different pitches in the two ears. If the condition continues over a period of years, the deafness often becomes more profound and no longer shows much variation in degree. The diplacusis and distortion are then no longer noticeable because of the severity of the deafness. Hearing tests are suggestive of a uniform nerve deafness in the affected ear.

2. Tinnitus nearly always accompanies the deafness, and this symptom is usually of a double nature, a high pitched ringing or hissing which is not bothersome and a low pitched pounding or roaring, often synchronized with the heart beat, which is most troublesome and, in some cases, is complained of as bitterly as the vertigo.

3. Labyrinthine activity. Caloric tests show either a non-functioning or hypoactive labyrinth on the affected side and the reaction to caloric tests frequently varies at different times. As a general rule, the more severe the deafness, the less the response of the labyrinth to the caloric test. The unaffected labyrinth will also usually show a diminished response to caloric stimulation. This is especially true of the vertical canals and would appear to be a physiological attempt on the part of Nature to balance or equalize the activity of the opposing labyrinths. These symptoms and signs are suggestive of a varying endolymphatic distention with an accompanying variation in

the sensitivity of the end organs involved. This accounts for the diplacusis, distortion of hearing, varying severity of deafness and tinnitus and the diminished response to stimulation of the labyrinth.

Hydrops of the labyrinth is a disease usually occurring in middle and later life. It seems to be more common in males than in females. There are frequently spontaneous remissions, wherein the individual may be free of attacks for months or even years, only to have them recur with increased severity. This condition is usually unilateral and affects only one labyrinth but, in approximately 10 per cent of the cases, the second labyrinth may become involved. Acute attacks may be brought on in one of two opposite ways. First, an increased pressure in one labyrinth may suppress its activity and result in a physiological over-reaction from the opposing labyrinth or, secondly, there may be a release or lowering of pressure in the distended labyrinth so that this labyrinth temporarily is overstimulated and upsets the balance control of the other one. A significant point in this respect is the observation that, during an attack, the hearing in the affected ear may markedly improve. This second reaction is not a common one and has been noted only a few times. Between the acute attacks there is usually some deafness, the low pitched tinnitus continues, and the offending labyrinth is hypoactive to stimulation. Patients frequently complain of a sense of imbalance or unsteadiness between the active attacks and of a feeling of pressure or fullness in the head. In many cases the fear of attacks is almost as bad as the attacks themselves so that these people are afraid to venture outside of their homes.

No attempt is made here to explain the etiology or underlying causes of hydrops of the labyrinth which are still unknown. In my experience medical treatment has rarely been successful in curing this disease, although it often alleviates the symptoms and enables the patient to tolerate the condition. I do believe that conservative therapy should always be tried. There are many and varied forms of treatment advocated, which in itself is indicative of the lack of effectiveness of any one form of treatment. It is interesting to note that, knowingly or unknowingly, the accepted forms of treatment all seem to have as their aim a lowering of the distention of the labyrinth. These include the use of histamine, nicotinic acid, sodium elimination or replacement and dehydration. The efficacy of any new form of treatment must be regarded with question until a large number of cases have been treated and over a considerable length of time because of the possibility of a spontaneous remission of the symptoms characteristic of these cases. In my experience treatment with small subcutaneous injections of histamine has been most effective in alleviating this condition, with gratifying results in about one-third of the cases. There are many cases which do not respond to conservative therapy, and this condition is so incapacitating that the patients become desperate and are willing to gamble on any kind of surgical procedure which has a chance of eliminating this distressing malady. The economic

phase also deserves consideration as many of these patients are unable to work or earn a livelihood.

Up to the present time the accepted surgical procedure for this condition has been sectioning of the vestibular nerve. It has been quite successful in a few expert hands. However, it is a hazardous undertaking and the results have sometimes been disappointing. Moreover, the low pitched grinding tinnitus is usually not alleviated, and some cases have cerebellar disturbances and difficulty with balance even though the acute, vertiginous attacks disappear. There is also the danger of injuring the facial nerve. Partial or total nerve section would seem to be an illogical procedure for this condition as it does not attack the seat of the trouble, namely, the hydrops of the labyrinth. I believe that any operation performed should be upon the labyrinth itself and should include opening the membranous labyrinth to release some of the endolymph. There have been few reports of labyrinth surgery for this condition. Portmann's [3] endolymphatic sac operation has relieved some patients, although the relief has often been only temporary and some of these cases had complete loss of hearing in the operated ear. In England the operation of choice until recently would seem to be alcohol injections into the labyrinth, either through the drum and oval window or through a trephine opening in the horizontal canal. This procedure causes complete destruction of the cochlea and vestibule and has not infrequently caused facial paralysis. It has found little favor in this country. Putnam [4] reported two cases in which he opened the superior semicircular canal by way of the middle cranial fossa and used a coagulating current to destroy the vestibule without destroying the cochlea. This procedure has merit but the approach is unnecessarily difficult and the cranial cavity need not be opened. In the past year Cawthorne [1] reported 50 cases in which, by way of the mastoid route, he opened the bony, horizontal semicircular canal and with fine tweezers removed the membranous organ. In some cases he also injected alcohol into the vestibule. In all of these cases there resulted a complete loss of both cochlear and vestibular function and the hearing was destroyed. However, his procedure has been received with favor because it has been effective in terminating the vertiginous attacks.

The ideal surgical procedure should be one which would be effective in terminating the vertiginous attacks and the tinnitus without destroying the hearing. This is one advantage of the partial nerve section operation since some of the hearing can be preserved.

The operative procedure which I am reporting is briefly as follows: A partial, simple mastoidectomy is performed by the postauricular route in which the mastoid antrum is opened widely and the outer wall of the aditus is removed far enough forward to expose the short process of the incus. With a small, motor driven burr the bony, horizontal semicircular canal is opened medial to the short process of the incus. The opening is made in this portion of the canal since it is near the ampulla and, through an opening at this point,

a needle can be passed forward through the canal into the vestibule. When the point of the needle strikes the anterior wall of the vestibule, it is then slightly withdrawn and pressed towards the medial wall so as to avoid the facial nerve. A light, coagulating current is then applied to the needle. The needle is withdrawn, a few "sulfa" crystals are dusted into the cavity, and the mastoid incision completely closed with clips. Clips are removed on the fourth day and the dressing usually discarded by the sixth day. I have employed this procedure on 11 cases of hydrops of the labyrinth in the past four years and I believe it gives promise of effectively terminating the vertiginous attacks and, at the same time, of preserving usable hearing in the operated ear. Nine of these patients had unilateral involvement and two had bilateral involvement. The elapsed time since operation has been from one to four years in eight of the 11 cases, and I believe sufficient time has elapsed for a true evaluation of results. In all cases to date the procedure has resulted in a complete loss of vestibular response to caloric stimulation of the operated ear. The hearing has varied markedly. In two cases there was total loss of hearing, but in one of these there was no attempt to preserve hearing as there was only residual hearing present before the operation. In four cases the hearing has remained at essentially the same level as before operation. Three cases show a further loss of hearing chiefly in the lower tones. Two cases show a marked improvement in hearing. In one of these cases, there was a uniform preoperative loss of hearing averaging 70 decibels, whereas, since operation, the hearing has returned to within normal limits and has remained so for two and one-half years. The nine patients with unilateral involvement have been completely free of vertiginous attacks since the operation. Some had almost immediate relief from vertigo, whereas in others it took from two to three months before the other labyrinth completely adjusted. The duration of postoperative vertigo and imbalance varied in direct proportion to the amount of labyrinthine activity in the affected ear before operation as shown by caloric tests. These nine patients have been rehabilitated and all have returned to their normal way of life and have been most grateful for the operation. Moreover, the low pitched, grinding tinnitus has been completely relieved in these cases although there has been little effect on the high pitched tinnitus which in some cases increased. None of these patients complained about the high pitched residual tinnitus. Three of them have stated that the pounding tinnitus before operation was as incapacitating as the vertigo. Using a noise apparatus to mask the hearing in the unaffected ear all nine cases could understand an amplified, conversational voice with the operated ear. In other words they all have usable hearing in the affected ear. In the two bilateral cases, the desired results were not attained. Unfortunately, these were the two cases in which complete loss of hearing resulted in the ear operated upon so that it was considered too much of a hazard to operate on the second ear, and they continued to have attacks from that ear, though one is responding to histamine and

gets along fairly well. I believe that the total loss of hearing in the operated ear of these two cases was due to technical mishaps during the operation, as a result of allowing a suction tip to come too close to the opening into the labyrinth in removing bone dust, with the result that the endolymph was entirely removed. I believe these mishaps can be avoided in the future. There were no postoperative complications in any of this series; all wounds healed by primary intention. Patients were well enough to be discharged from the hospital in from one to three weeks, depending upon the amount of postoperative physiological labyrinthitis in the unaffected ear.

In commenting upon the effect of this procedure I can only conjecture as to what actually happens inside the labyrinth. The original idea of using a coagulating current in the vestibule was to try to destroy the neuromechanism of the vestibule with as little damage as possible to the cochlea. The coagulating current may result in an actual coagulation of some of the endolymph. With a distended membranous organ, a needle passed into the vestibule would have to perforate the utricle. This mechanical perforation would cause a release of endolymph. Apparently the coagulating current tends to seal up again the opening in the membranous wall so that all endolymph is not lost and the cochlea can continue to function. It may be that the current destroys the nerve fibers of branches of the vestibular nerve to the utricle and superior semicircular canal which lie in the immediate vicinity of the end of the needle, while the needle itself has destroyed the horizontal semicircular canal in penetrating it. It is to be hoped that we may be able to obtain sections from some of these labyrinths for pathological examination at some future time.

Comment

No claim is made that this operative procedure is perfected. Nevertheless, our successes with it over the past four years make us believe that it is worthy of report, since it has proved successful in relieving the vertiginous attacks of Ménière's disease or hydrops of the labyrinth and has preserved usable hearing in nine of 11 cases operated upon to date. Animal experimentation and pathological examination of postoperative labyrinths are particularly desirable. The former is now being carried out by one of my confreres.

Conclusions

1. The term "Ménière's disease" should be used only to designate a hydrops of the labyrinth, a proved pathological entity.

2. This disease provides a clear cut, clinical picture which can be differentiated from all other conditions showing the Ménière syndrome.

3. The operative procedure here presented is still in its experimental stage.

4. The results in the above series of cases seem definitely to justify it as a surgical procedure for intractable cases of hydrops of the labyrinth.

5. It has proved successful in terminating the vertiginous attacks in such cases.

6. The effect on hearing has varied from restoration of normal hearing to a complete loss.

7. The low pitched, pounding or grinding tinnitus has been eliminated by this procedure, although high pitched tinnitus has sometimes increased.

8. This procedure seems to be preferable to that of sectioning the vestibular nerve in its results, simplicity and safety.

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THE EFFECT OF DORYL (CARBAMINOYLCHOLINE) IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASE*

By Gamliel Saland, M.D., F.A.C.P., Randolph Rosenthal, M.D., Charles Klein, M.D., and Herman Zurrow, M.D.,
New York, N. Y.

Carbaminoylcholine, known popularly as Doryl, is one of the most powerful parasympathomimetic drugs known. As a choline derivative, its properties causing general vasodilatation suggested its use in peripheral vascular disease. The literature is sparse with reference to its use in this connection. Starr,[1] in 1937, reported striking relief of rest pain except in the presence of gangrene or undrained purulent infection.

Chemistry and Pharmacology.[1, 2] Carbaminoylcholine chloride ($NH_2COOCH_2CH_2N(CH_3)_3Cl$) was first synthesized in 1932 by Kreitmair. Its actions parallel the effects produced by stimulation of the parasympathetic nerves such as general vasodilatation, drop in blood pressure, increased salivation, gastrointestinal peristalsis, uterine and vesical contractions, and sweating. In addition to the muscarinic effects of the drug, it also exhibits slight nicotinic effects on skeletal muscle and ganglion cells. Atropine neutralizes the muscarinic actions of the drug.

Plan of Study. This is a three year study of a group of 21 patients who were given biweekly injections subcutaneously of 0.25 mg. of doryl over periods varying from six months to three years. No patients with history or signs of asthma or chronic bronchitis were accepted for doryl therapy. The results of this treatment were compared with the results found in other controls receiving no specific therapy and studied for similar periods of time. Six additional controls were added to 30 others recorded in previous reports.[3, 4] We thus had a total of 36 controls similar in diagnosis and complications to the treated group. All patients in both groups were ambulatory and had a complete general and peripheral vascular study prior to the onset of doryl therapy. All were instructed in foot hygiene and care, diet, and general measures outlined in our clinic routine. All patients were reexamined and studied at six month intervals according to the following criteria[5, 6]:

I. *Vascular Anatomic Status:* This factor was determined by the evaluation of amplitude of vessel pulsation determined by palpation, temperature changes, rubor on dependency, pallor on elevation, and roentgen study for arterial calcification. This factor was graded from four plus, indicating severe involvement, to zero indicating no involvement.

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From the Peripheral Vascular Disease Department, The Bronx Hospital, Bronx, New York.

II. *Tissue Anatomic Status:* This was determined by the degree of involvement of the superficial and deep tissues and graded four plus indicating presence of gangrene, three plus indicating ulceration, two plus indicating infection without gangrene, and one plus when skin atrophy, muscle atrophy or nail changes were present; zero when no involvement was apparent.

III. *Rest Pain:* This refers to pain other than claudication. It includes neuritic pain, paresthesias, coldness or night cramps. This was graded four plus for severe pain, to zero for no pain.

IV. *Claudication:* This was measured as an index of the number of blocks the patient could walk before pain in the calves supervened. Four plus indicated that the patient could walk only half a block; three plus indicated patient could walk one-half to two blocks; two plus indicated two to four blocks; and one plus indicated more than four blocks; zero indicated absence of claudication.

V. *Vascular Reserve:* This was studied by means of the thermal vasodilatation test and complete nerve block (common peroneal and posterior tibial) where the first test failed to produce complete vasodilatation.[7] Vascular reserve was graded four plus indicating full vasodilatation by production of a rise in skin surface temperature of the big toe to 30.5° C.; three plus a 75 per cent rise from the initial temperature to 30.5° C.; two plus a 50 per cent rise; one plus a 25 per cent rise; and zero negligible or no rise.

VI. *Functional Classification:* This represents a composite evaluation of all factors.

Class I. Patients with organic disease without symptoms.

Class IIa. Patients with organic disease with minimal symptoms.

Class IIb. Patients with organic disease with moderately severe symptoms.

Class III. Patients with organic disease bedridden because of gangrene, infection or intractable pain.

Class IV. Patients with symptoms, without evidence of organic vascular disease.

Procedure. All patients who were placed on doryl therapy were first subjected to the following precautionary study. 0.125 mg. of doryl was injected subcutaneously and pulse and blood pressure readings were taken at five minute intervals for 30 minutes. If no untoward effects were noted, the study was repeated with a dose of 0.25 mg. of doryl subcutaneously. If there were still no untoward effects, patients were started on 0.25 mg. of doryl * subcutaneously biweekly. A loaded syringe with atropine sulfate gr. 1/100 was kept on hand for emergency use.

* We first used aqueous doryl containing 0.25 mg. per c.c. for the subcutaneous injections. We then attempted to prolong the effect by preparing stock solutions of doryl in oil at a concentration of 0.25 mg. per 0.50 c.c. for subcutaneous injections. This method was found dangerous because of the insolubility of doryl in oil. Several patients resultantly received an overdose of doryl with the following reactions: fainting, bradycardia, marked drop in blood pressure, marked intestinal peristalsis, salivation and sweating. These effects were immediately counteracted by the subcutaneous injection of atropine sulfate gr. 1/100. At this

Results

I. Six month study: After treatment with doryl for six months, three patients showed no improvement in vascular or tissue anatomic status, and no improvement in vascular reserve. Claudication was improved in two cases. None of these three patients had rest pain before or after completion of therapy. Of 14 control cases observed over a similar period, eight cases showed improvement of vascular anatomic status; three cases showed improvement of tissue anatomic status; six cases showed improvement of vascular reserve. Claudication was not improved. Rest pain was improved in two cases. Functional status was not improved in any case.

It will be noted that for this period results were promising only with regard to claudication in the doryl treated cases.

II. One year study: After treatment of seven cases for one year with doryl, no cases showed improvement of vascular anatomic status; one showed improvement of tissue anatomic status; three cases showed improvement in vascular reserve. Rest pain was improved in three out of four cases. Two cases showed improvement in claudication. Functional classification was essentially unchanged in this group. Of 19 control cases, four showed improvement in vascular anatomic status; one in tissue anatomic status; six in vascular reserve; five in claudication; four in functional status. Only one out of 16 manifesting rest pain showed improvement in this category.

Results in the group treated for one year suggest definite improvement in rest pain and equivocal improvement in vascular reserve in the doryl series.

III. One and a half year study: Of three cases under doryl therapy for one and a half years, none showed improvement in vascular or tissue anatomic status. One case was improved in vascular reserve; one showed improvement in claudication; and two cases in this series complaining of rest pain prior to the onset of therapy had no rest pain after therapy was completed. One case showed functional improvement. Of 12 controls, four showed improvement in vascular anatomic status; four showed improvement in tissue anatomic status; five showed improvement in vascular reserve; and six showed improvement in claudication. There was no case of improvement in rest pain where it was present in 10 of the 12 control cases. Six cases showed functional status improved.

Results in the one and a half year group suggest relief of rest pain as the only benefit from doryl therapy.

IV. Two year study: Six cases received doryl therapy for two years. Of these, one showed vascular anatomic improvement; one showed tissue anatomic improvement; three showed improvement in vascular reserve; one in

point, the idea was conceived of dissolving doryl in gelatin, in a liquid state which would form a slight nodule when injected subcutaneously (0.25 mg. doryl per 0.5 c.c. of gelatin mixture). The nodule would disappear in 24 hours. There was no further trouble with this method which was used until September 1943 when gelatin was no longer obtainable because of the war. At this point we reverted to the use of aqueous doryl 0.25 mg. per 0.5 c.c. for the balance of the study which ended six months later.

claudication; and none in rest pain (only one patient in this group had rest pain). None showed improvement in functional status. One control case showed no improvement in any category.

This group suggests improvement in vascular reserve when doryl was given over a two year period.

V. Three year study: Two cases continuing under doryl therapy for three years showed no improvement in any of the categories studied. None of the control cases continued beyond two years.

Complication and Special Study. One patient, 67 years old, developed typical peptic ulcer symptoms while under doryl therapy. The diagnosis of duodenal ulcer was confirmed by roentgen-ray. Doryl therapy was discontinued because of the possible relationship. A study of this factor was undertaken with 10 patients who were given fractional gastric analyses following alcohol test meal, and again following alcohol test meal plus a doryl injection of 0.25 mg. immediately after the alcohol meal. Specimens were taken during fasting, one-half hour after test meal and one hour after test meal. The same intervals were used for the doryl sitting. In two cases there was a significant difference in the free acid and combined acid determinations one hour after the beginning of the test. The half hour extractions failed to show significant differences in any of the 10 cases. Table 1 below illustrates the positive findings in the two cases.

TABLE I

	Alcohol Test Meal			Doryl Alcohol Meal		
	Fasting	30 min.	60 min.	Fasting	30 min.	60 min.
(1) Free HCl	0	54.0	43.6	8.8	40.0	67.0
Combined Acid	13.6	67.2	59.8	20.8	80.0	107.0
(2) Free HCl	14.0	36.0	35.0	0	20.0	72.0
Combined Acid	34.0	70.0	65.0	15.8	36.0	98.0

Summary. A group of 21 patients was studied from six months to three years while receiving biweekly subcutaneous injections of 0.25 mg. of doryl. It was found that compared with the control group of 36 cases, there were no significant differences in vascular anatomic status, tissue anatomic status, claudication, vascular reserve or functional classifications. Where, however, the control group had no improvement with regard to rest pain, doryl treated cases showed a definite relief of rest pain.

CONCLUSIONS

Doryl is a valuable drug whose application to peripheral vascular disease should be limited to the treatment of rest pain. It is contraindicated in patients with history or symptoms of peptic ulcer or asthma. Doryl should

be used only by those who are thoroughly acquainted with its pharmacology and its contraindications.

We gratefully acknowledge the technical assistance of Rosa Abraham, and the volunteer secretarial assistance of Leah Banks. Appreciation is also extended to Dr. H. Feibes of the Department of Gastroenterology for his assistance in the gastric analyses.

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THE INTEGRATION OF THE EXACT SCIENCES IN ALLERGY RESEARCH *

By Leslie N. Gay, M.D., F.A.C.P., *Baltimore, Maryland*

Some years ago Dr. Abraham Flexner of the Rockefeller Institute, in conversation with the late Mr. George Eastman, asked him whom he regarded as the most useful worker in science in the world. Mr. Eastman replied without the least hesitation, "Marconi." Dr. Flexner surprised him by saying, "Whatever pleasure we derive from the radio or however wireless and the radio may have added to human life, Marconi's share was practically negligible." Mr. Eastman, a far-seeing and philanthropic gentleman, was planning to devote his vast fortune to the promotion of education in useful and exact sciences. He asked Dr. Flexner for an explanation, and I quote Dr. Flexner's clearly thought out reply: "Mr. Eastman, Marconi was inevitable. The real credit for everything that has been done in the field of wireless belongs, as far as such fundamental credit can be definitely assigned to anyone, to Professor Clark Maxwell, who in 1865 carried out certain abstruse and remote calculations in the field of magnetism and electricity. Maxwell reproduced his abstract equations in a treatise published in 1873. Other discoveries supplemented Maxwell's theoretical work during the next 15 years. Finally, in 1887 and 1888 the scientific problem still remaining—the detection and demonstration of the electromagnetic waves which are carriers of wireless signals—was solved by Heinrich Hertz, a worker in Helmholtz's laboratory in Berlin. Neither Maxwell nor Hertz had any concern about the utility of their work; no such thought ever entered their minds. They had no practical objective. The inventor in the legal sense was of course Marconi, but what did Marconi invent? Merely the last technical detail, the now obsolete receiving device called a coherer, almost universally discarded."

What is true of the research of Heinrich Hertz may be said of the investigations of scientists the world over. Without electricity the world today would be helpless. Michael Faraday's discoveries of the induction of the electric current and the effect of magnetism on polarized light, together with even earlier studies in the field of electricity, have led to many practical applications of electricity by which our daily burdens have been lightened. In the domain of medicine and public health the principles of electricity have been utilized to great advantage to relieve suffering humanity. For example, one can mention the application of electricity to the production of the roentgen-ray so helpful in the diagnosis of disease, and more recently, in the treatment of inoperable cancer.

Until the onset of the present tragic conflict, scientists throughout the

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world have utilized, wherever possible, the discoveries of their peers, in order to solve their problems and to advance their theoretical hypotheses. This is true in medicine, a science which is made up of many separate fields awaiting research and investigation. As in the case of Marconi, so aptly discussed by Dr. Flexner, the clinician frequently adapts the scientific discovery of the laboratory investigator to the more practical side of medical science, and although I do not reflect critically on the ability of the clinician, who recognizes "the usefulness of useless knowledge," nevertheless more honor is due to the research student.

For the past 20 years I have been analyzing a branch of medicine which was given the name of "Allergy" by von Pirquet in 1906. This term is synonymous with the more explanatory word "hypersensitiveness." It refers to the condition of an individual who reacts specifically, and with char-

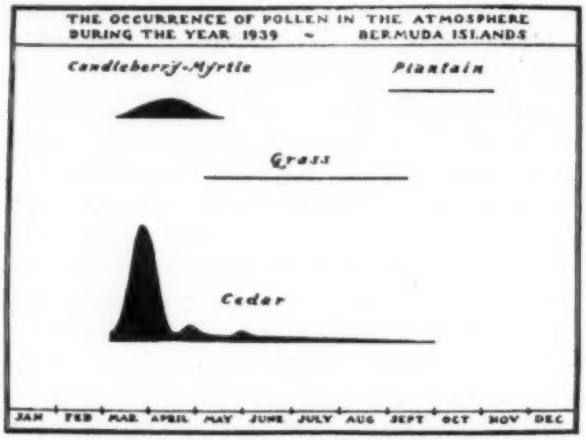
THE OCCURRENCE OF POLLEN IN THE ATMOSPHERE
DURING THE YEAR 1939 ~ BERMUDA ISLANDS
Candleberry-Myrtle
Plantain
Grass
Cedar
JAN FEB MAR APRIL MAY JUNE JULY AUG SEPT OCT NOV DEC

FIG. 1. Bermuda survey.

acteristic unusual symptoms, to contact with, or the administration of, a substance which when given in similar amounts to the majority of other individuals proves harmless (Louis Tuft, 1937). An example, the ingestion of egg white in most individuals produces no ill effects, but in a small number of persons violent reaction may occur even though the amount ingested is of microscopic size. Allergy is recognized through such common symptoms as those which are associated with hay-fever, asthma, hives, eczema, poison ivy, and other skin inflammations resulting from contact with primary or sensitizing irritants.

It is my purpose briefly to outline the relationship of the more exact sciences to this medical specialty and to demonstrate by these deductions how dependently related are the sciences in fields which might seem extremely remote one from the other. In order to study the many problems with which I have been confronted it has been necessary to resort to the knowledge dis-

closed by the botanist, the chemist and biochemist, the immunologist and physician of public health, the mechanical and electrical engineer, the industrialist, and more recently the legal profession.

It is quite impossible here to discuss in detail this remarkable specialty, which, by necessity, has applied so many diverse sciences to the solution of its problems. The greater part of our knowledge of those manifestations of human hypersensitiveness, grouped under the general term of *allergy,* is based upon the fundamental principles of anaphylactic reaction in lower animals. Anaphylaxis, demonstrated in 1904 by Dr. Theobald Smith, is a term applied to a state or condition which is produced by the following experiment: If a small amount of horse serum, perhaps 0.1 cubic centimeter, is injected into a normal guinea pig, no reaction will occur. If, however, after an "incubation" period of 14 days, a second larger amount (1 cubic centimeter) of horse serum is injected into the vein, the animal will show characteristic symptoms and usually will die in a very few minutes. The reaction thus produced is termed *anaphylactic shock.* Although human allergy and animal anaphylaxis resemble one another, there are two distinct and fundamental differences. First, human allergy may be inherited whereas animal anaphylaxis is artificially induced in the laboratory; second, in animal anaphylaxis the repeated injection of very small doses of the sensitizing serum will prevent the shock or death of the animal. Complete desensitization in human allergy on the other hand is most difficult and is rarely accomplished.

An excellent example of the serious reaction occasionally encountered in man is to be found in the prophylactic treatment of tetanus. It is common knowledge that any puncture wound should be looked upon as a potential case of tetanus. As a preventative it has been the universally accepted practice to give an injection of tetanus antitoxin. For years the antitoxin has been developed through the medium of horse serum. Consequently, the individual who might have inherited a sensitivity to horse serum has a violent and distressing shock reaction immediately after the prophylactic injection. Fortunately, in the majority of such instances serious results can be combated by appropriate medication. Nevertheless, these serious and occasionally fatal reactions have stimulated the biologist and biochemist to greater efforts in research and, fortunately, during the past decade the solution of the problem has been found. Tetanus toxoid has been developed without horse serum (the offending agent) and ample opportunity to test its effectiveness has been offered during the present war.

The procedure of administration differs somewhat from that which was followed in the prophylactic treatment with the antitoxin. In the latter case the antitoxin was administered after the wound had been incurred. The present method of prevention of tetanus in our armed forces is to administer a dose of toxoid immediately upon the induction of the soldier into the service, to be followed by a second dose after two months. Should the

soldier later receive a wound, his identification tag will state he has received preliminary prophylaxis and only a third supplementary dose will be necessary as soon as it can be conveniently injected. The success of this preventive treatment has been recently reported by the British and French armies. In the British Army the prophylactic treatment prior to Dunkirk was optional on the part of the soldier, but in the French Army the treatment was compulsory. Among 16,000 wounded British soldiers who had received prophylactic injections no tetanus occurred, while in 1,800 wounded who had refused treatment there were eight cases. On the other hand, among the thousands wounded in the entire French Army, all having received toxoid, but one case of tetanus developed.

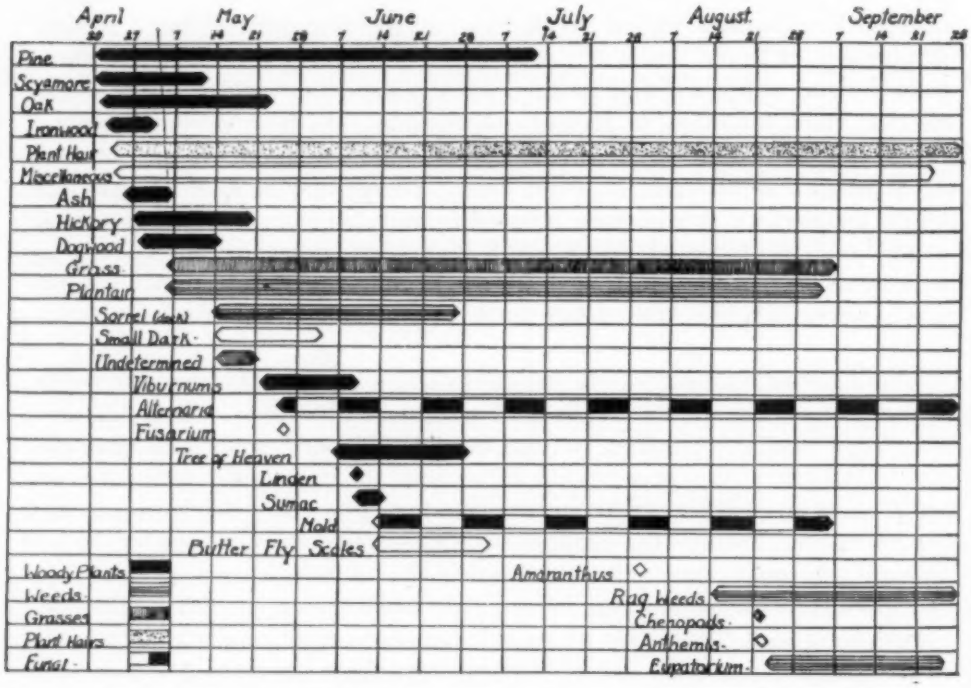

FIG. 2. The occurrence of pollen in the atmosphere during the year 1932, Baltimore, Maryland.

After the demonstration of anaphylaxis in animals, it was a natural development for the clinician to attempt correlation of the phenomenon with certain symptoms observed in the human subject. It was not until 1910 that the attention of immunologists was directed by Meltzer to the similarity of the marked distention of the lungs seen in the guinea pig and the pulmonary distention seen in patients with bronchial asthma. However, it was in 1819, nearly a century earlier, that Bostock, an English physician, described a syndrome which is a classical example of hypersensitiveness. I refer to the disease commonly spoken of as hay-fever. Bostock described this syndrome

as "summer catarrh" with a seasonal incidence and a distinct symptomatology. Elliotson, in 1831, referred to the fact that one of his patients developed the symptoms when flowers were in bloom, with the inference that the symptoms were due to pollen. This is the first reference in medical literature of this possibility. It remained for Blackley to confirm this supposition by a series of experiments, published in 1873. He was the first to apply the skin test, inoculating his own skin with dry pollen by the scratch method, and being a victim of this group of symptoms he obtained a large hive at the site of the impregnated area.

Since the excellent publication of Moore and La Garde in 1926, entitled "The Identification of Pollens from So-Called Hay-Fever Plants," in the Annals of the Missouri Botanical Garden, American allergists have given increasing attention to the pollen content of the air and to its relation to the incidence of hay-fever and asthma, and systematic surveys have been carried out in many sections of the United States. It was in 1929 that Acquarone and Gay published the first survey of the pollen flora of the Eastern Seaboard. Ordinary microscope slides, greased lightly with vaseline, were exposed out of doors. These slides, protected by a small metal shelter open at the sides, were collected after twenty-four hours' exposure and the number of pollen grains of each species of tree or plant was counted and identified. The keys developed by Moore and La Garde proved of great value in making identifications. It is obvious that pollen grains, which appear on the slides in considerable numbers, must be liberated from the freely flowering vegetation prevalent in the neighborhood. One has only to note what species are pollinating abundantly and to secure pollen of each directly from the anthus in order to obtain standards for comparison with those deposited on the slides. Pollen grains, the microspores of seed plants, possess, in common with plant spores in general, a high degree of specificity; that is, each species possesses distinctive spores. Since the characteristics of the spores are so definitely fixed in each species, it is possible to identify pollen grains with reasonable certainty.

The pollen season falls naturally into four subseasons: The tree season, March and April; the grass season, May, June; the plantain season, June, July; and the ragweed season, August and September. As a patient's clinical symptoms will parallel these seasons, it is quite easy to determine from the history which species of pollen is responsible for the discomfort. Confirmation of the cause is established by the intracutaneous or scratch test. Since 1929 an annual survey has been carried out in the Baltimore area and the schematic charts demonstrate the distribution qualitatively of the pollen in the atmosphere during the flowering seasons.

In spite of the knowledge obtained from the survey of the pollen flora, it is often impossible to relieve a patient who suffers from the symptoms associated with pollen inhalation by the usual specific treatment. A haven of refuge for those who suffer from the distressing symptoms, which result

from the inhalation of dry, wind borne pollen, has been sought for many years by patients in advertised areas of this continent. For a time the New England State, New Hampshire, seemed to answer all requirements; as civilization has moved into the secluded mountainous areas, many seeds of the offending grasses and ragweeds have been implanted in the fertile soil by the traveling public, and consequently there has been a decided "dropping off" in the popularity of the White Mountains as a region where those who suffer with these respiratory symptoms may find relief. Farther to the west, in Northern Michigan and in Southern California, one may sojourn in comparative comfort during the ragweed season. But other complicating factors, which are as disturbing as the ragweed pollen, may be encountered in these districts.

It is recognized that the continued influence of pollen on the mucous membrane of a sensitive individual depends upon several factors, such as temperature, barometric pressure, rainfall, prevailing winds, and the relationship of the land to the sea. Prevailing winds proceeding from the ocean cleanse the atmosphere; and, therefore, the relative location of land to sea is by far the most important factor in reducing to a minimum offensive pollen grains. This is true irrespective of the season of the year.

Because of their popularity with, and their accessibility to the citizens of the United States, the islands of Bermuda were chosen for a survey of the flora of the atmosphere. In the Bulletin of the Johns Hopkins Hospital, issued February, 1941, a report of the survey can be found.

In size the group of islands is slightly over 19 square miles, 15 miles long and three miles wide; the average width is somewhat less than one and a half miles. The average depth of soil on the islands is estimated to be six inches. The climatic conditions of Bermuda produce subtropical or warm temperature vegetation. Spring is the blossoming season for most annuals; but in the hottest days of August and the coldest days of January and February there are blossoms in every garden. Although there is a profuse growth, it is remarkable that only 8.7 per cent of the plant life is endemic. The large proportion has entered by natural agencies from America and the West Indies.

Because of the geographic and climatic advantages which seemed to be offered in Bermuda for the relief of pollen-sensitive patients, a survey of the pollen flora of the atmosphere suggested itself. A single season's record of the succession of species of pollen which invade the atmosphere of any given locality furnishes valuable information regarding its hay-fever potentialities. Each year the cycle faithfully repeats with only such minor fluctuations as may be due to seasonal variations. The survey was commenced March 1, 1939, and was concluded April 1, 1940. The same procedure described by Acquarone and Gay in 1929 was followed.

The conclusion is that there is available within easy travel distance of the United States a group of islands which has a constant year-round atmosphere

entirely free of the usual disturbing pollens of grasses, plantain and ragweed. Only during late February and March are there two trees, cedar and candleberry myrtle, which produce sufficient pollen to cause the respiratory symptoms of hay-fever and pollen asthma. The absence of the pollens so disturbing to countless citizens of the United States should make the Bermuda islands most popular during the spring and summer months.

The specific treatment of persons sensitive to pollens, namely, injections of the extract of the offending pollen in graduated doses, may fail to give the desired relief. It was essential, therefore, to try to find another means to bring comfort to these patients. An opportunity was afforded by a manufacturer of air-conditioning equipment to study the effect of air-conditioned atmosphere on individuals suffering with symptoms of hay-fever and pollen asthma. This treatment was a new method of approach and the results of the investigation were published in the Journal of the American Medical Association in May, 1933. The efficacy of the air-conditioning system used in the investigation was demonstrated most satisfactorily. Complete relief was given to patients suffering with hay-fever while they occupied the air-conditioned room. It was emphasized, however, that the relief of patients depends entirely upon the ability of the equipment to cleanse the atmosphere of offending pollen; the cooling feature is quite secondary, and is important only as a means to accomplish more perfect filtration and lend physical comfort to patients while occupying such an equipped room. To those individuals who can afford to install such a system, whether in the home or in the office, great relief can be assured.

After the demonstration that pollen can be filtered from the atmosphere by the use of air-conditioning units, other mechanical devices were sought to accomplish the same result. In 1935 Criep, of the University of Pittsburgh, published the clinical results which he obtained after he had "cleaned" the pollen from the air with an electrostatic unit developed by G. W. Penney. The unit was inexpensive and was designed to supply and clean 27,000 cubic feet of air per hour. The electrostatic air cleaner removes dirt and pollen by generating electrons in a high electrostatic field. These electrons tend to attach themselves to dust particles, thus giving the particles a negative electrical charge. When they touch the positively charged surface of a series of plates, the electrical force disappears and they are held by adhesion. This method efficiently removes pollen from the atmosphere, although its original purpose was to clean from the atmosphere minute copper particles, which often endanger workmen in industrial plants.

Respiratory distress of a violent type frequently results from a dust hazard little suspected by the average physician, and certainly not suspected by the engineer who originally designed the pipeless furnace method of house heating. It consists of one large central hall register through which hot air passes and distributes both dust and imperceptible gas from the first floor to the attic. Unfortunately its popularity because of its cheapness has been

widespread throughout the farming districts and small country towns. It is one of the common causes of winter asthma in both the child and the adult and must be looked upon as a serious health hazard. Relief of the asthmatic tendency is obtained after the removal of the "hot-air" system of heating.

Often patients subject to attacks of asthma, which develop from so many different causes, fail to respond to any of the commonly used therapeutic measures. Fortunately the physicist and mining engineer have contributed to medical science a chemical element, helium, which is most effective in relieving the asthmatic paroxysm. The story of helium is unique in the annals of science. Until 15 years ago it was obtainable only in very small quantities and then at the price of $2,500 a cubic foot. Today for about one cent a cubic foot an unlimited supply is available.

It was Sir Norman Lockyer who, by his development of spectroscopic investigation (Proceedings Royal Society, vol. 15, 1866) as applied to astronomy, established the fact that the sun spots are large magnetic centers and the prominences are masses of incandescent gas, mainly hydrogen, forming an envelope about the sun, the thickness of which is estimated to be 5,000 miles. A little more than 70 years ago, in 1866, this scientist while investigating the spectrum of the sun observed that eruptions from its surface gave bright lines in the yellow zone that were hitherto quite unknown in the sun or the laboratory. He was convinced that they were due to some substance in the sun unknown to the earth and for which he coined the name "helium," deriving it from the Greek name for the sun (*Helios*). He announced his discovery in October, 1868.

Lockyer's observations were made without the advantage of an eclipse of the sun. It is interesting that Janssen, a distinguished French astronomer, observing eruptions from the sun's limb in India in 1868 during a total eclipse, arrived quite independently at Lockyer's conclusion, and wired the French Academy of Science that he was of the opinion that the protuberances were composed of a gas that emitted the yellow spectral lines he had seen. Because of this joint discovery, announced coincidentally on the same day, one in England, the other in France, the French Academy had a medallion struck in 1868 commemorating it, bearing relief profiles and names of Lockyer and Janssen. There the subject rested until 1895 when William Ramsay freed a gas from the mineral cleveite and found in its spectrum the brilliant yellow line due to helium. Thus finally the gas was identified as a constituent of the earth and analysis revealed that it was a member of a group of gases known as non-reactive elements. Neon, used in "neon" street lights, is also of this group. These gases are colorless, noninflammable and nonexplosive. Next to hydrogen, helium is the lightest known substance, and is liquefied with the greatest difficulty.

Practical application of helium was delayed for many years until it was discovered in conjunction with natural gas in large quantities in the United States. A few small deposits were found in Kansas in 1903 and in 1928

the great wells near Amarillo, Texas, were discovered. Our government has since stored millions of cubic feet of the refined gas for military and commercial uses.

One of the most important and recently adopted uses for helium is in deep sea diving and caisson construction.* When a diver descends into the sea, or when a man is at work in a caisson, increased amounts of air are taken up by the body tissues, and because air contains 20 per cent oxygen and 80 per cent nitrogen, the absorption of nitrogen is particularly large. When the pressure is reduced, the excess amount of oxygen can be readily taken care of in the body tissue by ordinary combustion, but the nitrogen excess tends to separate and form gas bubbles.

If a diver is raised or "decompressed" too rapidly, he may develop "caisson" illness or the "bends," characterized by severe body pain, unconsciousness and even death, as was observed by Paul Best in 1878. It is necessary, therefore, to raise the diver slowly until the nitrogen has had time to escape through the lungs during respiration. The usual time necessary for a diver to descend to a depth of 200 feet is three to eight minutes, but after remaining at this level for 45 minutes, at least two hours will be required to bring him to the surface without distressing illness. Since Hildebrand knew that helium is the least soluble gas, the idea occurred to him to substitute helium for nitrogen in the gaseous mixture for divers to breathe. The sinking of a submarine with the loss of an entire crew suggested to our Navy that by analyses and research our physicists could enhance the usefulness of this gas. Hildebrand's impressions were confirmed. Because of its high rate of diffusion, moving three times more swiftly than nitrogen, it is liberated with greater rapidity from the lungs, thus proving its usefulness during the "decompression" of deep sea divers. Its practical application was assured and demonstrated when helium played a major rôle in the rescuing of our sailors from the *Squalus* submarine disaster.

The use of helium mixed with oxygen as a therapeutic gas was reported by Alvan Barach in 1934. He suggested its applicability in the treatment of asthmatics. Substituting helium for nitrogen in the air, the specific gravity of this mixture compared to that of the air is 0.34. The rate of diffusion of helium is three times that of nitrogen and the molecular weight is 4, while that of nitrogen is 28. Since respiratory work is in general proportional to the pressure of the air, the physical effort by the patient, or the pressure required to move helium-oxygen mixtures in and out of the lung, should be decidedly less than that incurred when breathing nitrogen-oxygen (air) mixtures. Striking diminution in the respiratory effort of an asthmatic patient is observed immediately when a mixture of helium and oxygen is inhaled. The vicious circle caused by lack of oxygen and respiratory

* Professor J. H. Hildebrand, of the University of California, and Drs. R. R. Sayers and W. P. Yant, of the U. S. Bureau of Mines, published a comprehensive treatise on this application in 1928.

fatigue is interrupted and, equilibrium being restored, the life of the patient may be saved.

We are living in an age which demands the prevention of disease rather than its cure. New methods of industry have rapidly developed, and new products have required in their manufacture the most complex chemical agents. Consequently the industrialist has encountered among his workmen manifestations of diseases which 20 years ago rarely presented themselves to a physician. Industry has been conscious of the hazards of these processes and is well aware that efforts must be made to eliminate them. I wish to refer briefly to industrial diseases, many of which may be classified under the head of "contact dermatitis."

Since the founding of the School of Hygiene at The Johns Hopkins University in 1918 the prevention of disease has been most emphatically impressed upon the physician, and indirectly upon the industrialist. Students from all parts of the world have learned how to combat and control epidemic diseases and also how to safeguard employees from hazards in occupation. Industrial medicine has attained a position of great importance, and management now recognizes the advantages of healthy personnel. The most prevalent industrial disease today is an inflammation of the skin termed "contact dermatitis." It is by no means a new problem, for as early as 1700 Bernardino Ramazini published a compilation of industrial diseases, mentioning the swollen hands of the baker due to wheat flour and the itch which developed from the dust of cereal infected with a then invisible parasite. Even today "grain itch" is very common among the handlers of wheat, rye, corn and linseed meal, if these cereals harbor their minute parasites. Scattered contributions have appeared in the literature on the subject since 1900. In 1928 the United States Public Health Service created a special department for the study of occupational dermatitis and named Dr. Louis Schwartz as its director. This is an important office, as 70 per cent of all occupational diseases are due to skin injuries.

There is a curious predisposition to occupational dermatitis. Dark skinned racial groups have proved less susceptible to skin irritants, this being well illustrated by the negro. Certain individuals unfortunately have skin characteristics which predispose them to irritants. A dry skin can not withstand the action of alkalis and solvents as well as a thick oily skin; on the other hand, an oily skin is more susceptible to the action of tar, pitch and petroleum products.

The chemical agents which cause occupational dermatitis may be divided into two groups, the primary irritants and the specific irritants. The chemicals which will produce an inflammation on any skin if allowed to remain in contact in sufficient concentration for the necessary length of time comprise the first group, and the second is composed of those which affect a comparatively small number of workers only after they have been sensitized or have become allergic to the irritant following previous exposure.

The primary irritants are both organic and inorganic—alkalis, acids, solvents, essential oils, dye intermediates, tar, pitch and petroleum products. From these irritants the industrial workers constantly require protective measures.

The specific sensitizing irritants likewise are numerous, and are encountered in such industries as those which employ the furrier, the dyer, the weaver, the leather worker, the oil worker, the manufacturer of cosmetics, the painter, the worker in plastics, and in many other trades. Especially among the fabric dyers and handlers of plastics, the use of complicated and synthetically prepared compounds adds to the difficulty of tracing the offending agents. Recently it has been discovered that certain chemicals, which come in contact with the skin or which gain access into the circulating blood by ingestion, may produce an unusual pigmentation because of the phenomenon of photosensitivity. Exposure to light produces such a change in the character of the material on or in the skin that it may be extremely irritating. A striking example is found among the men who work with pitch in the conduit industry. Exposure to sunlight produces an inflammation with pigmentation of the skin. As long as the worker remains indoors no serious reaction occurs. Recovery from the disease depends upon the use of protective clothing; even though the irritation diminishes the pigmentation is usually permanent.

CHART I

Chemical Primary Irritants
General Irritants

Inorganic			
Acids and Salts	Sulphuric Nitric Arsenous Etc.	Alkalis	Sodium Hydrate and Carbonate Potassium Hydrate and Carbonate Etc.
Salts of Irritant Metals	Mercury Chromium Arsenic Etc.		(Sensitization Usually an Important Factor)
Organic			
Acids Anhydrides and Salts of	Acetic Carbolic Formic Oxalic Picric Salicylic Etc.	Solvents	Hydrogenated Phenols Turpentine Formaldehyde Xylol Chloroform Etc.

CHART II

Specific Irritants Which Cause Dermatitis in Those Sensitized by Previous Exposure

Explosives	Photo Developers	Biologic Agents
Cosmetics	Soaps	Bacteria
Oils (Vegetable and Mineral)	Rubber Compounds	Parasites
Fur Dyes	Insecticides and Fungicides	Fungi
Leather Dyes	Fabric Dyes	
Photosensitizers	Resins and Waxes	

A similar reaction occasionally is precipitated after the ingestion of the barbiturates and with the addition of the sulfonamides another source of photosensitivity has been encountered.

It has been suggested that this unusual reaction is produced by changes in the physiologic porphyrin present in the skin, although other factors are probably involved.

The prevalence of occupational dermatitis has necessitated rigid and careful examination of prospective employees. If an individual is "sensitive" or allergic to a chemical agent which can not be avoided in a chosen occupation, he should not be subjected to a hazard which might incapacitate him for weeks. By a simple test, known as the "patch test," many industries determine whether a new worker can safely handle sensitizing irritants. A small amount of the chemical is placed on the skin and a fluff of cotton is placed over it, held firmly by means of non-irritating adhesive. Within 48 to 72 hours, the area is examined, and if the worker is likely to have trouble from contacts associated with his new occupation, a characteristic red vesiculating eruption will be observed under the adhesive. It would be extremely unfortunate for this individual if he were employed in such an environment.

As a consequence of these unusual features associated with contact dermatitis, certain criteria have been prepared as a guide to industry by the American Society of Dermatology and the American Board of Allergy. It has been necessary to have them because of the confusion which has arisen in the minds of the legal profession in compensation decisions. Gross negligence in the protection of workmen from well known primary irritants should entitle them to compensation, but there is a grave doubt as to whether they should be compensated for some hereditary or allergic defect for which no employer is responsible.

In this brief discussion I have outlined the ramifications of a minor specialty of medical science, allergy, with the more exact sciences. If one desires to advance in a chosen field, regardless of the specialty, a broad horizon is open to the student of research as well as to the clinician. Neither can accomplish the ultimate without a knowledge of development and progress in other fields. The association of members of a university faculty, the teaching of graduate students, and the instruction of undergraduates all tend to stimulate us to freedom of thought. So long as this freedom is defended and maintained, there need be no limit to scientific progress.

THE CLASSIFICATION AND NOMENCLATURE OF LEPROSY WITH SUGGESTIONS FOR A SIMPLIFICATION OF BOTH *

By HARRY L. ARNOLD, JR., M.D., and IRVIN L. TILDEN, M.D.,
Honolulu, Hawaii

THE classification of leprosy has had two almost wholly independent origins, one largely clinical, the other largely biological, and both in part bacteriological. The two have never been reconciled with each other, principally because the clinical leprologists and the dermatological leprologists have never learned to speak one another's language. This linguistic barrier is a remarkable one, the importance of which has not been fully appreciated. It has frequently stood, not only between these two different groups of students of leprosy, but also between the clinical leprologists and their own understanding of the disease.

In an attempt to remove this barrier, we will consider the problem under the following headings: (1) the clinical classification of leprosy; (2) the dermatologic classification of leprosy; (3) the South American dermatologists' classification of leprosy; and (4) leprologic nomenclature. It is our thesis that there is no fundamental incompatibility among these three classifications, and that they can be reconciled with one another, and greatly simplified, by little more than a change in the nomenclature.

THE CLINICAL CLASSIFICATION

The older clinical classification of leprosy, as described by Morrow [1] in 1894, divided the disease into two forms according to its localization: "tubercular" (or "tegumentary") if the skin and mucous membranes were the site of most of the lesions, and "anesthetic," "trophoneurotic" or "nerve" leprosy when it involved primarily the peripheral nerves. He added that "the two forms . . . exhibit marked differences in their external characters, mode of evolution, course, and termination." By 1910, according to Stelwagon,[2] the names "tubercular" and "anesthetic" had become established, in dermatologic literature at least, as the names for these two varieties of the disease, though Ormsby [3] more recently advocated the term "maculo-anesthetic," coined by Hansen and Looft, for the latter form of leprosy.

Regardless of the labels used, however, it is apparent all along the line that two different forms of the disease, not merely two different sites of involvement, were being distinguished. Indeed, the difference is so marked that Bateman,[4] in 1818, discussing *elephantiasis Graecorum* with its

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From the Department of Dermatology and the Department of Clinical Pathology, The Clinic.

"tubercles of the face . . . flattened nose, round eyes," wonders if the *leuce Graecorum,* with its "pale colour . . . and its loss of sensibility . . . be not [a] modification of the same disease." We have since learned, of course, that it is.

At all events, the clinical classification officially adopted at Manila in 1931 [5] divided cases of leprosy into two great groups: "neural" and "cutaneous." The quotation marks are intentional, and will be used wherever these words appear in what follows, for the reason that "neural" in the leprologic sense does not always mean neural (i.e., neurologic), and "cutaneous" in the leprologic sense does not always mean cutaneous (i.e., dermatologic). Nor does the third, minor group in this classification—"mixed" leprosy—mean mixed neurologic and dermatologic disease—for almost every case of leprosy, of whatever type, presents combined neurologic and dermatologic lesions, whereas it is extremely doubtful, as we shall see, whether any case of leprosy ever presents combined "neural" and "cutaneous" involvement in the leprologic sense of those words.

Lepromatous leprosy ("*tubercular*" *or* "*cutaneous*" *leprosy*). In 1938, at Cairo, leprologists were sufficiently impressed by the confusion resulting from their special use of the term "cutaneous," to be induced to abandon it; they substituted for it the term "lepromatous." [6] This form of leprosy is characterized by (1) involvement of the skin and mucous membranes and almost invariable involvement of the nerves (as well as of the lymph nodes, bone marrow, spleen, etc.; (2) abundance of *Mycobacteria leprae* in the lesions (except in rare recovered cases); and (3) generally rather rapid progression and an unfavorable prognosis. The patient regularly fails to react to intradermally injected lepromin.

This form of leprosy is indicated by the letter "L." It is important to realize that despite its names, it is capable of producing deformities due to nerve damage, which may be far more conspicuous than the associated skin lesions.

"Neural" leprosy. This form of the disease, the one formerly called "maculo-anesthetic" leprosy, stands in the strongest contradistinction to lepromatous leprosy, and not merely by reason of its moderate predilection for involvement of peripheral nerves. "Neural" leprosy is chacterized by (probably) invariable involvement of peripheral nerves, and usually of the skin as well; by the presence (except during transitory "tuberculoid reactions") of few or no demonstrable *Mycobacteria leprae* in the lesions; and by a generally slow course and a favorable prognosis. The patient regularly reacts strongly to intradermally injected lepromin.

This form of leprosy is indicated by the letter "N." Again it is of the greatest importance to realize that despite its name, it can produce skin lesions which may be many times more conspicuous and spectacular than the deformity caused by the associated neurologic lesions.

Mixed leprosy. There has been admitted, for some mysterious reason,

a third clinical group, sometimes set apart from the rest, though officially it is merely a subgroup of the lepromatous type: "mixed" leprosy, indicated by the initials "LN." It is said to include properly those cases of the lepromatous ("L") type in which neural (i.e., neurologic, as distinct from "neural") changes have supervened. Wade does not seem wholly to approve of this rather remarkable group, since in discussing it,[7] he has referred to the fact that cases of leprosy are "always in a sense 'mixed.'" Strictly speaking, since "N" cases are by definition those usually showing few or no bacilli, and "L" cases are by definition those showing many bacilli, persons with "mixed" ("LN") leprosy must be in the peculiar position of having a poor immunologic reaction to *Mycobacterium leprae,* and a strong one, simultaneously. It is as if a patient should have tuberculous sarcoidosis (Besnier-Boeck-Schaumann's disease), and pulmonary tuberculosis with caseation necrosis, cavitation and positive sputum, at one and the same time.

Altogether, it seems likely that this category of "mixed" leprosy is a hangover from the days when it was called, not "lepromatous-neural" ("LN"), but "cutaneous-neural" ("CN")—in other words, when its name suggested (however erroneously) that it might properly include all lepromatous cases showing fairly obvious evidence of nerve damage. Few leprologists now believe that a patient may have both "neural" and lepromatous types of leprosy simultaneously, although some believe that, rarely, transition may possibly occur from one to the other.

Varieties of "Neural" Leprosy

It was thought necessary in 1938, at the Cairo conference, to subdivide "neural" leprosy into three subgroups. This subdivision has been a bone of contention; agreement on it is by no means general, even today. The three official subgroups are (1) anesthetic (indicated by "Na"), (2) simple macular ("Ns"), and (3) tuberculoid ("Nt").

Purely neural ("anesthetic") leprosy. The anesthetic subgroup ("Na") includes all "neural" cases characterized by polyneuritic changes only. They regularly show thermal anesthesia (and probably also, if it is looked for, localized anhidrosis), less regularly tactile anesthesia, still less regularly pinprick anesthesia (analgesia); they may also show muscular weakness, paralysis, atrophy or contracture. They do not, by definition, present skin lesions other than purely trophic ones: malum perforans, for example; or atrophy or scaliness; or dermographism (with no flare about the wheal). Nerve trunks may be thickened and nodulated, and histologically often show (even in their finer cutaneous branches!) typical tuberculoid (sarcoid-like) granulation tissue, with few or no bacilli; the anesthetic skin areas, however, may on the other hand show only banal perivascular inflammatory changes, or none at all.

Simple macular ("maculo-anesthetic") leprosy. The "simple macular" subgroup ("Ns") includes those cases presenting the above manifestations

and, in addition to them, hypopigmented (or less often hyperpigmented) macules. These are called "simple macules" by leprologists, because their "macule," unlike the dermatologists' macule, is not necessarily a flat, impalpable lesion; it may be a beefy, indurated, sharply elevated plaque. Like lesions of the preceding subgroup, those of this type may show either banal perivascular round-cell infiltration (usually with a sprinkling of epithelioid cells) or, more often, frank tuberculoid granulomatous architecture. Wade and his associates,[8] Lowe [9] in Calcutta, the Russian leprologist, Stein,[10] and Saunders and Giffen [11] in the Virgin Islands, have shown that tuberculoid architecture can be demonstrated in many "simple macules," and in almost all such lesions when they are erythematous or their borders slightly papular. Ermakova,[12] in Moscow, also found suggestively tuberculoid changes in these lesions, though they were interpreted in the conclusions as banal inflammation.

Tuberculoid leprosy. The third subgroup, the tuberculoid ("Nt"), consists of those "neural" cases in which the skin lesions are papules, nodules, plaques, or elevated annules, poor or lacking in acid-fast bacilli (except during transitory exacerbations known as "tuberculoid reactions"), and presenting on histologic examination characteristic tuberculoid—sarcoid-like—architecture. These lesions are the "neuroleprides" of Unna, the infiltrated "leprids" of the older leprologists, and the tuberculoid "macules" of modern leprologists—"macules," notwithstanding their being elevated. They are for "neural" leprosy what the leproma or "nodule" is for lepromatous leprosy: the distinctive infiltrated granulomatous cutaneous lesion.

In summary, then, the orthodox clinical classification of leprosy recognizes only two principal varieties: the lepromatous type, with abundant bacilli and a poor prognosis, and the "neural" type, with few bacilli and a good prognosis; the latter type is further subdivided into anesthetic, macular and tuberculoid varieties, on almost exclusively clinical grounds. It is of the utmost importance, for a clear understanding of the disease, to realize that lepromatous leprosy attacks both the skin and the peripheral nerves (as well as other tissues), and that "neural" leprosy *also* attacks both the skin and the peripheral nerves. It is indeed perfectly possible, and by no means rare, to see advanced lepromatous leprosy of nerves with minimal skin involvement, or advanced "neural" leprosy of the skin with minimal nerve involvement. It must be plain from this, that some other and more apt word than "neural" is urgently needed for this group of cases of leprosy.

The Dermatologic Classification

The biologic-dermatologic classification of leprosy was initially propounded by Jadassohn in 1898.[13] He established three categories: the "typical leproma," the "typical (macular) neuroleprid" (without granulomatous changes, at least in the skin), and the "tuberculoid granuloma." These might be briefly designated as "lepromatous," "simple inflammatory,"

and "tuberculoid." Presumably Jadassohn omitted any "simple anesthetic" or purely neural group because he could always classify such cases on a histologic basis as either "simple inflammatory" or "tuberculoid."

As we shall see presently, this "simple inflammatory" group is the most troublesome of all; the criteria for its diagnosis are not well established; they consist rather of a lack of adequate criteria for classification in either of the other two groups. We may recall in this connection that much evidence has been adduced by Wade et al.,[8] Lowe,[9] Stein,[10] Saunders and Giffen,[11] and perhaps also Ermakova,[12] in support of the view that many cases which might be regarded by some students as "simple inflammation" really belong in the tuberculoid group. One is led to wonder whether most "simple inflammatory" cases—which have in common with the tuberculoid group a lack of bacilli, a strong immunologic response, and a good prognosis —may not be in fact tuberculoid cases in which the tuberculoid histologic architecture is simply immature.

The South American Classification

The Latin American dermatologists have written voluminously on the subject of leprosy in general and its classification in particular. We may briefly consider here what two of their principal spokesmen have had to say on the subject.

Rabello, Jr.,[15] of Brazil, proposed in 1936 a system which, while superficially similar in nomenclature to the orthodox one, actually differed from it fundamentally in spirit. He appeared to believe that the dualistic theory was untenable, and that there was no fundamental difference between the macule (or the leprologic "macule"?) and the leproma, either clinically, or in their evolution, or histologically, and that transition from macule to tuberculoid plaque to leproma might occur and frequently did. He also believed that tuberculoid and lepromatous lesions might coexist in the same patient, due to local differences in tissue immunity. This nihilistic unitarian theory was and still is, of course, quite inacceptable to most leprologists.

Pardo-Castello,[16] of Havana, has recently published a much more acceptable classification. It begins, unhappily, by dividing the disease into leprosy of skin, leprosy of nerves, and leprosy of other organs: a clinically obvious but misleading and basically meaningless division. Each of these is then subdivided into lepromatous, simple inflammatory, and tuberculoid subgroups—the same pattern as that advocated by Jadassohn.

He defends the simple inflammatory subgroup on the ground that it is a clinically as well as a histologically indeterminate one, cases of which may subsequently become either lepromatous or tuberculoid. It appears, however, from our observations and from the work of others, that the transition from bacteriologically negative simple inflammatory lesions to lepromatous ones is rare, whereas the transition from simple inflammatory lesions to tuberculoid lesions is very common. Indeed, as previously stated, many

cases classified even on histologic grounds as simple inflammatory may be shown by more intensive study (and perhaps a slightly higher index of suspicion) to already present tuberculoid architecture.

Aside from this supposedly indeterminate group, which at all events appears to be only a temporary pigeonhole for any given case, it is thus clear that Pardo-Castello's version of the Latin American classification is essentially the same dualistic one as the current official classification, with the word "tuberculoid" used in place of the word "neural." If the Latin Americans were willing to make their primary division of the disease into "lepromatous" and "tuberculoid" types (even retaining, if they insist, an intermediate indeterminate group), and *then* divide each of these into leprosy of skin, leprosy of nerves, and leprosy of other structures, their view of the disease would be essentially identical with that of the clinical leprologists elsewhere.

In the light of recent demonstrations of tuberculoid changes in simple macules, and the comparative rarity of a transition from these to lepromatous leprosy, and in view of the regular demonstration of tuberculoid changes in nerve trunks and branches in cases of purely neural "neural" leprosy, it would seem that the clamor might all be stilled by this simple compromise: merely substitute the word "tuberculoid" for the word "neural" as a designation for all cases of leprosy that manifest scanty bacilli, strong immunologic response, general tendency to more marked involvement of nerves than of skin, slow progression, a good prognosis, and perhaps, in borderline or histologically indeterminate cases, a positive skin reaction to lepromin.

Leprologic Nomenclature

The terminology of leprosy, as it has developed in the hands of clinicians, chiefly without special dermatologic or histologic training, has become an amazingly confusing affair. A table indicates some of the more confusing special meanings attached by leprologists to certain terms:

Word	Dermatologic Meaning	Leprologic Meaning
Neural	Characterized by involvement of nerves	Characterized by scanty bacilli and a good prognosis
Nodule	Circumscribed induration of skin up to about 1 cm. in diameter	Nodule of lepromatous granulation tissue, rich in acid-fast leprosy bacilli
Macule	Circumscribed impalpable alteration of skin color	Circumscribed alteration of skin color, frequently anesthetic, flat or elevated, with few or no acid-fast bacilli in the tissues
Mixed leprosy	Leprosy involving both nerves and skin (*this is erroneous*)	Leprosy of combined "neural" and lepromatous types Also widely employed in the (erroneous) dermatologic sense, but only for application to *lepromatous* leprosy with both nerve and skin involvement

All four of these terms have contributed importantly, by virtue of their highly restricted leprologic meanings, to the current widespread lack of understanding of clinical leprosy. The word "neural," for example, familiar to physicians generally as meaning "pertaining to nerves," has prevented them from going enough further to find out that it means, to leprologists, a relatively benign form of leprosy. The word "macule," similarly, has been taken at its face value by general practitioners talking to leprologists or reading leprosy literature; they have not generally realized that it applies to *any* circumscribed skin lesion, whether flat or elevated, of the relatively benign form of leprosy. "Nodule," in like fashion, has not been fully appreciated as the hallmark of the progressive, relatively communicable form of the disease. And of "mixed leprosy," perhaps the less said the better, for it seems apparent that neither dermatologists nor leprologists really know for certain whether it means lepromatous leprosy of both nerves and skin (and is, therefore, almost exactly as common as lepromatous leprosy itself), or whether it means combined lepromatous and "neural" leprosy of the skin, or of the nerves, or both—and is, therefore, exceedingly rare if not actually nonexistent.

Thus these terms, although they have long and satisfactorily represented to clinical leprologists the existence of two diametrically opposed forms of leprosy, have done precisely the opposite service for the physician whose contact with leprosy is casual and occasional. For him this fundamental distinction has been glossed over, almost as if deliberately. The distinction for him is all "nerve" versus "skin" leprosy; and if a little more intimate acquaintance with the disease teaches him that virtually all cases present *both* nerve and skin involvement, he is apt to feel that his clinical grasp of the disease is reasonably thorough. If he then learns that "neural" leprosy is frequently bacteriologically negative, who can blame him if he thinks he has learned that this is generally true of leprosy involving nerves?

If "cutaneous" was a misleading and confusing name for what is now called "lepromatous" leprosy, then by the selfsame token "neural" is a misleading and confusing term for the other form of the disease. It confuses general practitioners; it confuses dermatologists; and in some connections and in some quarters, at least, it confuses leprologists. It urgently needs to be replaced; and in the light of the studies to which we have referred, the word "tuberculoid" would seem to be the logical term with which to replace it.

Summary

The orthodox leprologic classification of leprosy divides the disease into "lepromatous" and "neural" forms, with the latter further subdivided into anesthetic, macular and tuberculoid types.

The biologic-dermatologic classification of leprosy divides the disease into lepromatous, macular (simple inflammatory) and tuberculoid forms, of

which the latter, and many, if not most, cases of the "macular" type, correspond to the "neural" group of the orthodox leprologists.

The South American dermatologists' classification divides the disease basically into lepromatous, nonspecific and tuberculoid forms; there is evidence to suggest that many, if not most, cases of the non-specific type may belong in the tuberculoid group.

Current leprologic literature contains four seriously misleading terms: "neural leprosy," "macule," "nodule," and "mixed leprosy."

The primary requisites of a new nomenclature and a new classification of leprosy are that they shall represent clearly, and not to the specialist alone, the fact that there are two types of leprosy: the one generally strongly bacteriologically positive, the other negative or almost so; the one with a bad prognosis, the other a relatively good one; the one relatively communicable, the other probably only slightly so if at all; the one with a negative cutaneous reaction to lepromin, the other with a positive one; the one histologically a granuloma composed almost wholly of bacillus-laden histiocytes, the other histologically showing aggregates of epithelioid cells and lymphocytes, often in the form of epithelioid tubercles.

If the word "neural" be replaced by the word "tuberculoid," the terms "nodule" and "macule" and "mixed leprosy" can then gradually be dropped entirely in their restricted leprologic sense and standard dermatologic nomenclature can generally be permitted to enter into leprologic literature freely, instead of only gradually as at present.

Conclusions

The present orthodox classification of leprosy is confusing in its detail and misleading in its nomenclature, but it is fundamentally compatible with both the biologic-dermatologic classification and with the South American dermatologists' classification.

The three could be reconciled by the adoption of a classification containing two categories: lepromatous leprosy and tuberculoid leprosy.

This would promote a much clearer understanding of the fundamental behavior of the disease, and would enormously simplify the classification and evaluation of individual cases.

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A CURRENT VIEW OF THE RABIES PROBLEM *

By J. CASALS, M.D., *New York, N. Y.*

FOR the past 15 years the number of human cases of rabies in this country has averaged 55 per year. In animals, incomplete data obtained from state departments of health [1] would indicate that for the period 1936–1940, the number is over ten thousand per year. The incidence of the disease in man and lower animals is greatest in the Southern and East-North-Central states, and in California.

Owing to its relatively high incidence in domestic and wild animals as well as to its dreadful clinical reaction, rabies, even though infrequent as a cause of death in man, constitutes an important public health problem.

The first question that comes to mind concerning rabies is: What are the chances of man's contracting rabies following the bite of a rabid animal? This all-important question must remain unanswered. Owing to the universality of the Pasteur treatment there are no modern statistics showing man's susceptibility to this malady. The older calculations are unreliable, extremely variable, and of little value. Thus, mortality following bite by a presumably rabid dog is stated as ranging from 2–50 per cent or even higher.[2] We know, however, that there are certain circumstances which will affect the rate of mortality among individuals who seek antirabies treatment. The location of the bite, for example, is very important. Bites on the head and neck result in the highest rate, followed by bites in the upper extremities, lower extremities, and trunk. Among other factors which strongly influence the outcome are the species of animal inflicting the bite, the number and depth of the wounds, the interposition of clothing, and the age of the individual.

It will be well to mention at this point that of persons who are given antirabies treatment following a bite by a rabid or suspect animal, about 90 per cent report bites by dogs, 5 per cent by cats, and the remainder by cattle, horses and other species.

Three aspects of the rabies problem are of immediate practical interest namely, diagnosis, prevention, and complications following treatment.

Diagnosis. Diagnosis of rabies in human patients is not a difficult clinical problem. The characteristic symptomatology plus evidence of a recent animal bite does generally permit an accurate diagnosis. Death follows in all cases. The problem of diagnosis in dogs or other animals is complicated. The clinician sees it in the following way: A person has been bitten by a dog; is the dog rabid? The answer to this question is important since it will

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From the Laboratories of the Rockefeller Institute for Medical Research, New York.

decide whether antirabies treatment has to be applied or not. Since, as we shall see later, complications may follow the treatment, one should not give it unless reasonably indicated. The observation of the dog may give to an expert veterinarian a fairly accurate answer. In general, however, it will be necessary to observe the animal for eight or 10 days before one can be certain. If the dog survives, rabies is excluded, whereas if death ensues the probability is that the dog was rabid.

However, it is for the laboratory to decide whether or not the animal had rabies. No methods at present available are satisfactory because they depend on the death or sacrifice of the animal. Serological reactions which would permit a diagnosis during life of the animal have not been developed. The methods at present in use are (1) histological examination of the brain of the animal, and (2) inoculation of cerebral tissue from the suspect into laboratory animals.

Animals infected with rabies virus exhibit in their brains typical microscopic lesions; particularly, the large pyramidal cells of Ammon's horn show Negri inclusion bodies. Negri bodies have special characteristics so that their identification is simple. They are always found in the cytoplasm, have a typical inner structure and special staining properties. Their presence establishes the diagnosis.

The other method for the diagnosis of rabies consists in the inoculation of a suspension of brain tissue from the suspect animal into other animals. All mammals are more or less susceptible to an intracerebral inoculation of rabies virus, but the animal of choice is the mouse.[3] Special strains of albino mice are highly susceptible to rabies and uniform in their response. The method of diagnosis consists in inoculating five or six mice intracerebrally with a suspension of brain tissue. In positive cases these mice will show signs of central nervous system involvement within seven to ten days and die usually within the next 24 hours. The brains of these mice exhibit Negri bodies. Of these two methods the latter is more accurate than the former. In a recent survey obtained by the Georgia State Board of Health, of 771 animal brains found positive for rabies on mouse inoculation, 81 or 10 per cent were negative for Negri bodies.[4] On the other hand all suspect animals that had Negri bodies on inoculation into mice yielded rabies virus.

Prevention. Preventive measures against rabies infection are: (a) general, which aim at the eradication of rabies at its source, with the purpose of destroying rabies reservoirs and preventing the spread of rabies from animal to animal or animal to man; (b) individual, which have as their goal the prevention of the disease in man after exposure.

Since dogs are the main source of rabies in this country, general measures for the control of the disease should be directed toward them. They are within the functions of public health officials. Muzzling of dogs, destruction of stray animals and strict quarantine are the three main steps. Such procedures have proved their efficacy on several occasions. Thus, a country

like Australia has been kept free of rabies because of the enforcement of quarantine laws. In England relaxation of the ordinances on muzzling and leashing has been found to result in a sharp increase in the number of cases of rabies.

Prevention of rabies in dogs by means of vaccination has been advocated as a method of diminishing the general incidence of the disease. In order to evaluate the efficacy of canine antirabies vaccination we depend on two kinds of data; those deriving from field observation and those from experiment. Field data are usually difficult to appraise properly; though incidence of rabies among dogs apparently diminishes following large-scale vaccination, no critical analysis of the results is available at this time.

What is recorded in the literature up to 1938 on animal experiments, as surveyed by Webster,[5] offers very little to support the claim of the efficacy of antirabies vaccination. In recent years, however, new methods have been developed for the study of the potency of rabies vaccines with the result that we have nowadays not only more effective vaccines but also more precise means of determining their value.

By means of the mouse test it has been possible to study the variables which influence the potency of vaccines. Their elimination has served, therefore, to improve the antigenicity of the latter. The strain of rabies virus used in the preparation of the vaccine, the animal species in which the vaccine is propagated, the age of the animals employed, the nature of the agent used for the inactivation of the virus, the length of time during which the vaccine is usable, are all important factors.

Vaccines for dogs consist of emulsions of rabies infected brain tissue in physiological salt solution in concentration of either 20 or 33 per cent. These suspensions are inactivated by adding some chemicals, usually phenol or chloroform. Such vaccines cannot contain any active virus according to regulations of the United States Bureau of Animal Industry. The dose is usually 5 c.c. per dog.

The efficacy of vaccines for use in dogs can be determined in the laboratory by the mouse test. This consists essentially in vaccinating mice with the test material, then infecting them, along with untreated controls, with a range of dilutions of fixed rabies virus. The challenge dose is given intracerebrally and by comparing the titer of the virus in the vaccinated and control mice one has an index of the potency of the vaccine.

Results of experiments in dogs in this laboratory indicate that 5 c.c. of vaccine per dog may not be sufficient to protect against heavy infection. It is probably true that the experimental is a more severe test than the natural infection so that this amount of vaccine may be sufficient in most cases. It would be advisable to give a second dose of 5 c.c. in order to establish a more solid immunity. How long immunity following vaccination lasts in dogs has not been determined. It is our experience that the potency of rabies vaccines as prepared for market has improved considerably in the past few years. Vaccines for use in man can be similarly tested.

In man vaccine is given following exposure, as a preventive treatment. The incubation period of rabies in man is, on the average, 30 to 60 days. Since the effective immunity following vaccination is established in a shorter time, the usual procedure in persons exposed to a rabid animal consists in starting vaccination as soon as possible after exposure.

There are different types of vaccines for human use, some of which contain active virus, others of which contain only inactivated virus. The original Pasteur vaccine is employed at present only in very few places. This method consists in the use of desiccated rabbit cords infected with rabies virus. Beginning with a cord dried for 14 days containing no active virus, successive injections are given in the next 13 days with cords that are dried for fewer and fewer days progressively until the last injection which contains fully active material.

At present inactivated virus is used as vaccine in man. Such vaccines consist generally of a 4 per cent brain suspension inactivated by different chemicals. One of the vaccines most commonly used in this country and abroad is the Semple vaccine in which phenol in concentration of 0.5 per cent is employed as inactivating agent; in other vaccines formalin, ether, or chloroform is added or heat is used. Fourteen injections of 2 c.c. each are usually given. In special cases both the number of injections and the amount of vaccine are increased.

A great deal of material has been accumulated in the past 15 years regarding the effect of vaccination in human beings. McKendrick has collected statistics from most Pasteur Institutes throughout the world and analyzed them very carefully. In his latest review [6] over 1,000,000 cases of human antirabies treatment were analyzed. A number of interesting facts were revealed. The mortality among those people who were given the treatment was 0.33 per cent; this low figure cannot be taken as a real index of the value of rabies vaccination because the degree of exposure among people varied markedly. Of the four categories of treated individuals, the greatest number fall in the groups in which exposure to rabies has not been proved or is doubtful. Another startling fact which emerges from McKendrick's analysis is that no vaccine surpassed others tested, with the possible exception of a slight apparent superiority of one containing active virus, although even in this instance the statistical analysis gives no conclusive proof. Moreover, the promptness with which antirabies treatment was begun did not influence the outcome; indeed, contrary to general belief, McKendrick revealed that in a group of 581,519 Europeans, those whose treatment was begun immediately to four days after exposure showed a higher mortality rate than those treated later. In fact, when immunization was delayed eight to 14 days, the chances of survival were greater. Among 321,348 non-Europeans, no disadvantage was apparent in delaying treatment up to 14 days after exposure.

Nevertheless, in spite of these rather puzzling data, treatment should be recommended in all cases of proved or suspected exposure to rabies. Owing

to the low mortality rate found in people who have had the Pasteur treatment as well as to the low incidence of complications following rabies treatment, this is the most logical procedure.

Complications. Complications of different types are unusual following antirabies treatment. For the most part they are mild, consisting of local reactions at the site of inoculation, with erythema, edema, pain, pruritus and tenderness. The side reactions are of minor consequence, and should not stop treatment.

More severe reactions may follow, such as peripheral neuritis and dorso-lumbar myelitis. The latter may arise gradually with fever and weakness; recovery is the usual outcome. Treatment should be discontinued in the presence of such signs.

Finally the most severe complications are the paralytic accidents, often of a Landry type, with high fever, headache, nausea, vomiting, urinary retention and ascending paralysis of lower extremities. Paralysis may continue to ascend involving the bulbar nuclei. Recovery may occur in the milder cases and sometimes permanent disability is a sequel. Death follows in about one-third of these cases. In McKendrick's analytical review there are listed 181 paralytic accidents in a series of 1,060,832 treatments (one in 5861); of those 48 were fatal (one in 22,100). It must be pointed out here that paralytic accidents are more frequent following use of vaccines containing active than inactivated virus. Thus McKendrick shows that paralytic accidents developed in one person of 3398 after treatment with attenuated virus (cords), one of 3194 after treatment with diluted virus, whereas the incidence was one of 8,887 following phenol-inactivated vaccine and one of 17,620 following heat-killed vaccines.

Since any definite superiority of one vaccine over others has not as yet been demonstrated, a vaccine should be selected on the basis of minimal possible post vaccinal complications; those containing only inactivated virus should, therefore, be chosen.

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CASE REPORTS

MALARIA COMPLICATED BY PNEUMONIA; TREATMENT WITH SULFADIAZINE AND ATABRINE*

By Z. Taylor Bercovitz, F.A.C.P., Lt. Col., M.C., A.U.S.

The purpose of this paper is to report the case of a patient suffering with *P. falciparum* malaria complicated by pneumonia and successfully treated with both atabrine and sulfadiazine. The clinical picture of the onset of pneumonia confused the picture by suggesting a relapse of the malaria. The diagnosis was cleared up by physical examination.

Case Report

E. D. S., a white male, 53 years old, was brought to the attention of the writer because during what was presumably a relapse of malaria he failed to respond to the administration of quinine. The patient was an engineer who two weeks after his return from Africa, where he had gone 10 weeks before, complained of feeling tired. He had had a chill, his temperature rose to 103°–104° F. for two to three days, and he had watery stools. Blood smears for malarial parasites were positive, and the diagnosis of *P. falciparum* malaria was made. The patient was given quinine, 30 gr. daily for about four days. The temperature fell to about 100° F. at the end of that time, and the quinine dosage was reduced to 10 gr. a day.

Within a day or two the temperature began to rise again and the patient began to have a dry cough. He complained of pain in the lower left axilla. It was at this time that the writer was called in for consultation. Examination of blood smears confirmed the diagnosis of *P. falciparum* malaria made by the attending physician. On physical examination signs of lobar pneumonia were discovered over the left lower lobe. The quinine was discontinued, and a dose of 0.3 gm. atabrine was given immediately. Sulfadiazine therapy was instituted also, 2.0 gm. immediately and then 1.0 gm. every four hours thereafter, day and night, a total of 12 gm. having been given before the patient was admitted to a hospital on April 5, 1942, 10 days after the onset of his malarial symptoms.

On admission the patient was acutely ill and delirious. There seemed to be no apparent benefit from the sulfadiazine therapy. Roentgen-ray on April 6 confirmed the diagnosis of lobar pneumonia of the left lower lobe.

Sputum examination showed type 7 pneumococcus. The blood level of sulfadiazine on April 6, after the administration of a total of 12 gm. of the drug, was 12.9 mg. per 100 c.c. Sulfadiazine, 1 gm. every four hours, day and night, was continued, and 200,000 units of type 7 antipneumococcic rabbit serum were given intravenously. The patient was also started on atabrine, 0.1 gm. daily.

Repeated examinations of the urine were negative. Blood cultures taken on several days were negative. The percentage of hemoglobin varied from 54 to 72. The red blood cell count ranged from 2,900,000 to 3,940,000 per cubic millimeter. The white blood cell count on admission was 5,750 per cubic millimeter, and subsequently

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From the Department of Medicine, New York Post-Graduate Medical School and Hospital.

the count fluctuated between 4,100 and 7,000 per cubic millimeter. The differential count showed 43 to 77 per cent polymorphonuclear neutrophiles, 18 to 53 per cent lymphocytes, and 1 to 9 per cent monocytes. On several days, myelocytes, metamyelocytes, polymorphonuclear eosinophiles and basophiles were evident. In view of the low hemoglobin and blood elements, the patient received three blood transfusions of 500 c.c. each on April 6, 9, and 16. He was also given ferrous sulphate and liver extract during his illness.

In all, the patient received a total of 59.5 gm. sulfadiazine over a period of 12 days. The sulfadiazine was discontinued on April 14. During the period of administration the sulfadiazine level of the blood ranged from 4.3 mg. per 100 c.c. on the day the drug was discontinued to 13.4 mg. per 100 c.c. on the fifth day of administration. The atabrine, in a dosage of 0.1 gm. daily, was given for 22 days, and discontinued on April 27. On April 22 the patient was started on anayodin, three tablets (0.25 gm. in each), three times a day, which was continued until May 4.

Blood smears for malarial parasites were negative on April 8 and thereafter. The temperature fell to normal the day after admission, and then rose to 101.4° F. the next day and remained over 100° F. for three days. It then fell to normal where it remained until April 26, when it rose to 102.4° F. This rise was attributed to the occurrence of obliterative pleurisy at the left base.

Inquiry into the patient's past history revealed that he had had an attack of left sided pleurisy in 1917, and then in 1924 during a severe cold or grippe roentgen-ray showed "a spot on the lung" on the left side, which was still present on roentgen-ray later.

The patient was discharged on May 13, 1942 free from malarial and pneumonic symptoms. Roentgenogram still showed slight productive changes at the left base and elevated left diaphragm with partial obscuration of the left costophrenic sinus, suggesting old, pleuritic thickening at the left base.

When he was discharged from the hospital he was given atabrine tablets (0.1 gm. in each), with instructions to take one daily for the following 60 days. This plan was faithfully carried out, the patient having been seen at the office at weekly intervals for almost one year. During that time no relapses of malaria occurred. In the interim the patient made another trip to a malarial country in the tropics. While on that trip and for 60 days subsequently he took one tablet of atabrine (0.1 gm.) daily. Repeated thick film examinations of blood were negative for malaria.

Discussion

It is evident from the facts that the onset of the pneumonia was at first considered a relapse of the malaria. It was only because the patient failed to respond to quinine that the writer was consulted. Careful physical examination revealed the presence of lobar pneumonia of the left lower lobe and ruled out the malarial relapse. This emphasizes the need for careful physical examination during malaria and watchfulness for the occurrence of other diseases which may obscure the diagnosis.

It is significant that the atabrine therapy, although continued for 22 days in a daily dosage of 0.1 gm., did not interfere with the therapeutic efficacy of sulfadiazine in the pneumonia, nor did the latter conflict with the value of the atabrine in controlling the malaria. Following the initial course of treatment with atabrine, the patient was given a daily dosage of 0.1 gm. for 60 days, and subsequent to this when on a trip to a tropical country he took atabrine daily while on the trip and for 60 days thereafter. Under this régime, there was no relapse of the malaria, and the blood continued to be free of malarial parasites on repeated

monthly examinations after discontinuing the atabrine. When discharged from the hospital the patient was able to carry on his duties as an engineer.

It is interesting to note, with reference to the therapeutic compatibility of atabrine and sulfadiazine, the experience of Harned and Cole.[1] These investigators observed that quinine administered orally with sulfapyridine to rats increased the total amount of sulfapyridine absorbed and the amount excreted in the urine in the form of conjugated crystalline acetylsulfapyridine. Consequently, the authors concluded:

"In view of the close similarity between the conjugation and excretion of sulfapyridine in man and the rat it appears that treatment in the human of a double infection for which quinine and sulfapyridine would be simultaneously used should be managed by other drugs until it is established that the quantities of these drugs employed in human therapy do not increase the hazard of urolithiasis."

However, when atabrine, which in the treatment of malaria is used in approximately one-tenth of the weight employed for the salts of quinine, was substituted for quinine in these rat experiments, the excretion of sulfapyridine was not affected.

Sulfathiazole was used simultaneously with atabrine without any untoward effects in a case of *P. falciparum* malaria with concurrent right lower lobe pneumonia which the Standard Oil Company [2] was good enough to bring to the attention of the writer. This patient was treated at the Caripito Hospital of the Standard Oil Company in Venezuela, and was the only case reported in response to a request by the Standard Oil Company that its South American physicians report any cases in which pneumonia and malaria existed simultaneously in the same patient treated with one of the sulfonamides and at the same time with atabrine or plasmochin. This patient received 0.1 gm. atabrine three times daily for seven days, a total of 2.1 gm., followed by 0.01 gm. plasmochin three times daily for the subsequent three days, and then 5.0 gr. quinine sulfate three times daily for a week. During this time, a period of 17 days, the patient received a total of 55 gm. of sulfathiazole. This case progressed satisfactorily to a rapid recovery, without complications due to the medication he received.

The results obtained in this case and in the case described by the writer suggest that in man sulfadiazine or sulfathiazole may be used in conjunction with atabrine for the treatment of pneumonia during a malarial attack.

Summary and Conclusions

1. A case of malaria complicated by pneumonia is described.

2. Atabrine therapy of the malaria did not in any way influence the effect of sulfadiazine on the pneumonia in the case reported by the author.

3. The daily administration of 0.1 gm. atabrine for 22 days while under treatment for the pneumonia and for 60 days on two occasions subsequently, did not adversely affect the patient.

4. The experience in the author's case suggests that atabrine may be used safely simultaneously with sulfadiazine.

5. Reference is made to a similar case treated with atabrine and sulfathiazole with no untoward effects.

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"METASTATIC" CALCIFICATION IN SOFT TISSUES OF LEGS IN OSTEITIS DEFORMANS; CASE REPORT *

By BERNARD SELIGMAN, M.D., F.A.C.P., and LOUIS NATHANSON, M.D., M.Sc. (MED.), *Brooklyn, New York*

SOFT tissue, "metastatic" calcification has been reported in only one previous case of osteitis deformans, which was described by Wells and Holley.[1] Metastatic calcification is to be distinguished from calcinosis. The former represents calcification of apparently healthy tissue due to changes in the composition of the blood calcium and phosphorus salts, phosphatase, or alkalinity. The latter represents another stage of an underlying pathologic process of certain tissue such as occurs in scleroderma, sclerodactyly, Raynaud's disease, dermatomyositis, progressive lipoid dystrophy, myositis ossificans, etc.[2]

In a 59 year old man who had Paget's disease for six to seven years and had received 10 minims of ergosterol, activated 10,000 times, daily for 15 days, Wells and Holley found at autopsy extensive metastatic calcification of the lungs, of the kidneys, of the gastric mucosa, of focal areas in the skin, of the endocardium of the left atrium, extensive calcification of the anterior leaflet of the mitral valve and of the cusps of the aortic valve. No gross evidence of renal insufficiency was noted. Microscopically the skin showed heavy focal calcium deposits in the subcutaneous tissue surrounded by a fibroblastic reaction with many young fibroblasts and foreign body giant cells.

In the individual herein described extensive calcium deposits were seen radiographically in the soft tissues of both legs as well as in the larger blood vessels of the torso; and numerous negative centered faceted stones were identified on roentgen-ray examination of the gall-bladder. This patient had received small doses of viosterol and calcium over a period of one and one half years. She had evidence of decompensated arteriosclerotic heart disease with edema of the legs of eight years' duration.

CASE REPORT

E. M. was known to have had Paget's disease for six years in November 1935, when she was under the care of Dr. Leo Mayer at the Hospital for Joint Diseases. Two months previously she had stepped off a trolley car and felt pain in the region of her left hip and groin. Roentgenograms taken at this time were not available to us. These areas were not tender but were painful on weight bearing. She had been almost entirely confined to bed following this accident. The pain was relieved after a rest of four weeks in bed. She was also given 10 grains of calcium lactate, five minims of viosterol three times a day and received ultraviolet irradiation of the entire body for 21 days.

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From the Jewish Sanitarium and Chronic Hospital, Brooklyn, New York.

Her grandmother had Paget's disease. One of her sisters was a diabetic. The patient had had diphtheria at the age of 17 and had suffered from many sore throats over a period of years. She was married in 1916 and had two children in 1921 and 1924, both of whom were delivered by Cæsarean section. With the second a hysterectomy was performed and a large fibroid removed. After the latter she developed postpartum fever and a phlebitis of both lower extremities.

Before admission to the hospital she complained of dyspnea on exertion and orthopnea, and had nocturia as well as edema of the ankles. Her blood pressure was elevated to 170 mm. Hg systolic and 110 mm. diastolic. She had systolic murmurs at the apex and base of the heart. She had pulsations over the entire precordium. The legs showed a pitting edema. These persisted for the rest of her life.

She was seen by one of us (BS) February 12, 1936 at the age of 57. For several months she had complained of constipation, belching, heartburn, and epigastric distress when she walked after eating. This was more evident after she became stouter. She had frequency of urination and would get up two to three times a night to urinate. For one month she had a headache. She had been deaf for three years. She complained of stiffness, was drowsy, and fell asleep easily.

FIG. 1. Roentgenogram of skull.

She was keen in her responses, mild and soft spoken. The head was carried forward with the chin resting on her chest. It was symmetrical and markedly enlarged, with the broad end up. The face was triangular in outline. The temporal arteries were markedly tortuous and prominent. The vision was so poor in her left eye that she could not count fingers. She had bilateral nerve deafness; the ear drums were dull, thickened and gray, and all the landmarks were obliterated. Her hearing was markedly impaired, more so on the right side, and only a loud voice from the left side was audible. Her teeth were carious and many were missing. The right supratonsillar area was scarred. The veins in the neck were distended. The chest was markedly enlarged. The breasts were enormous in size. The heart was markedly enlarged, and she had a pulsation of the entire precordium. A systolic murmur was

heard over the aortic and mitral areas. The abdomen was markedly obese and flaccid. Two scars of the previous operations were noted. The back was squat and crushed in on itself. She had pitting edema of both legs. She had moderate bowing of both tibiae. No limitation of motion of the hip joint was found. She was not tender over the left hip or groin, but stated that these areas were still painful on weight bearing. She had marked sclerosis of the vessels of the wrist. No clubbing nor cyanosis of the fingers was noted. Her blood pressure was 160 mm. Hg systolic and 70 mm. diastolic to 150 mm. Hg systolic and 100 mm. diastolic. She was placed on a restricted diet and lost 12 pounds, from 219 to 207.

She continued to take 7 minims of viosterol and 40 grains of calcium lactate daily for a period of one and one half years. She received in all 3,957,120 I.U. of vitamin D. The only complaint which could be attributed to the calcium deposits, found later

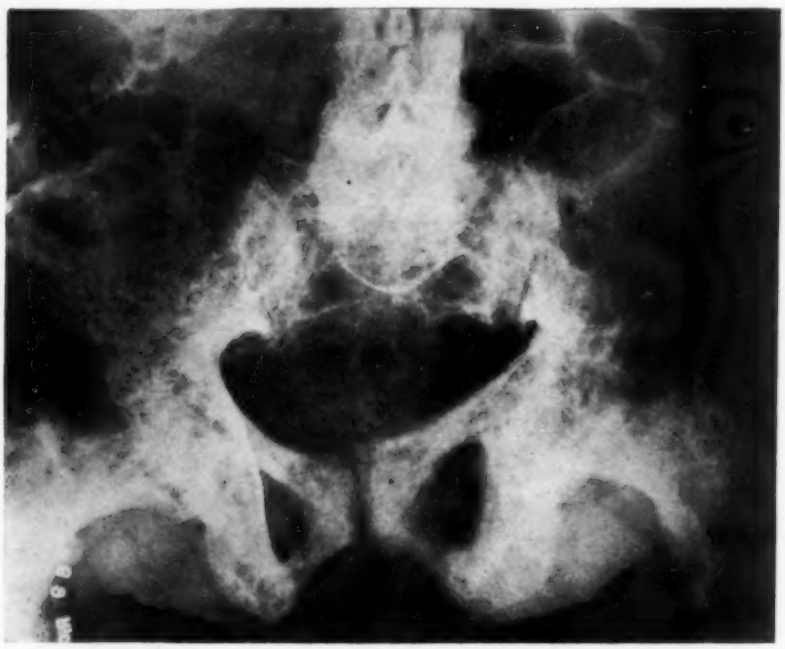

FIG. 2. Roentgenogram of pelvic bones, gall-stones and calcification of aorta.

on roentgenographic examination of the legs, was a tenseness of the skin; however, her legs were edematous. In March 1939, she was admitted to the Coney Island Hospital because she developed a bronchopneumonia; type three pneumococcus was found in the sputum. While walking around during her convalescence, she slipped and fell, fracturing her left femur. At this time Dr. Emanuel Mendelson was able to observe on roentgen examination numerous areas of calcification in the subcutaneous tissues of the leg particularly posteriorly. On July 1, when the fracture healed and she was able to get about on crutches, she was transferred to the Kings County Hospital. Later she became bedridden and was admitted to the Jewish Sanitarium and Chronic Hospital on August 28, 1939. She used two pillows when she slept, was constipated, had non-bleeding piles, frequency and urgency of urination and incontinence for one year.

November 27, 1939 she fell out of the wheel chair in the bathroom without any obvious fracture. April 30, 1940, she developed transient signs of a cerebral thrombosis in the left cortical region. In January 1942, she developed stubbornness and uncoöperative behavior which may have been due to vascular involvement of the frontal lobes. In December 1942, roentgenograms revealed multiple fractures of both legs and ankles with a deposit of lime salts in the soft tissues. She refused permission for skin biopsies. Several weeks later she had signs of a hypostatic pneumonia with an enlarged tender liver. She vomited for one week. The digestive disturbance disappeared following digitalization. Her pulse was irregular at times, and the heart rate varied from 66 to 104 per minute. She developed a febrile reaction with pains in the abdomen on September 17, 1943. She died suddenly on October 6, 1943. No autopsy was permitted.

Laboratory Findings

Blood	Hosp. Jt. Diseases	Coney Island Hospital		Jewish Sanitarium		
	November 1935	March 1939	June 1939	August 1939	May 1940	April 1943
Calcium	9.6	9.6	9.5	8.8		10.7
Phosphorus	5	6.25		5.4		4.5
Phosphatase	68.2		35.7	24.1		26
Uric acid	4.6			2.6	3.7	
Sugar	106	150	81	109	120	
Urea	10			13.4	16	
Cholesterol		270				
Esters		131				
Creatinine	1.2			1.1	1.2	
Red blood cells (in millions)			4.86	4.1	3.6	4.1
Hemoglobin			85%	90%	74	10 grams
White blood cells			8,500	10,500	8,300	6,700
Polymorphonuclear leukocytes			70	70	67	53
Lymphocytes			28	29	33	41
Eosinophiles				1		
Transitionals			2			5
Blood pressure	170/110	120/70	132/80		134/80	126/64
Urine						
Specific gravity		1018	1012–30	1014	1036	1018
Albumin	Trace	Faint trace				
Red blood cells						50–60/hpf
White blood cells	Occasional	20–30/hpf	1–15/hpf			
Casts						Hyaline and granular
Crystals	Triple phosphates with alkaline, calcium oxalate with acid urine			phosphates	phosphates	

Roentgenographically, there was evidence of advanced Paget's disease of all the skeletal structures. The disease appeared to be most marked in the skull, pelvis, spine and lower extremities. The skull was tremendously enlarged, had a scaphocephalic configuration with considerable flattening. A platybasia effect was present owing to the softening and flattening of the base of the skull on the cervical spine. The skull

and facial bones resembled those in leontiasis ossium. The maxillary, ethmoidal and sphenoidal sinuses were obliterated by the overgrowth of bone. The bones of the base of the skull were dense and eburnated. The same alterations were present in the temporal bones. In addition to the advanced distortion of the pelvis due to Paget's disease there was a flattening and deformity of the hips producing a coxa vara configuration.

FIG. 3. Roentgenogram of right leg showing calcium deposits in soft tissue.

The examination of the lower extremities showed evidence of Paget's disease of the bone, but in addition showed extensive calcification of a granular and mottled type within the soft tissues. This was most marked in the subcutaneous tissue and extended through the muscle planes particularly along the mesial and posterior surfaces of the lower extremity from below the level of the knee to above the ankle joint. The calcification was somewhat more marked in the 1942 examinations than in those made in 1939. No soft tissue calcification was present in the upper extremities.

Moderately advanced calcification was present in the abdominal and pelvic vessels, but no calcification in the popliteal or tibial vessels at the level where the soft tissue calcification was found. Several fractures of both lower extremities were present which healed normally. The soft tissue calcification was apparently not related to the fractures in so far as we could determine. Numerous negative centered faceted gall-stones were present in the gall-bladder. Minimal calcification was present in the thoracic aorta and mottled changes could be demonstrated through both lungs,

FIG. 4. Roentgenogram of left leg showing calcium deposits in soft tissue.

many of which had a circumscribed appearance suggesting calcification within pulmonary vessels. We were, however, by no means certain of this. The heart was tremendously enlarged in all its diameters during the entire period of her observation.

An electrocardiographic tracing on March 10, 1942 showed ventricular premature contractions, left axis deviation with slurring of QRS_2. On December 30, 1942 fibrillation was present, and all the QRS complexes were of low voltage. The chest findings remained the same until April 14, 1943 when a patch of pneumonia developed at the left base.

The final diagnosis was Paget's disease, arteriosclerotic heart disease associated with hypertension, cardiac failure and auricular fibrillation; cerebral and coronary thromboses with a terminal bronchopneumonia. She had, as accompanying features, bilateral nerve deafness, gall-stones and calcification of the soft tissues of the legs.

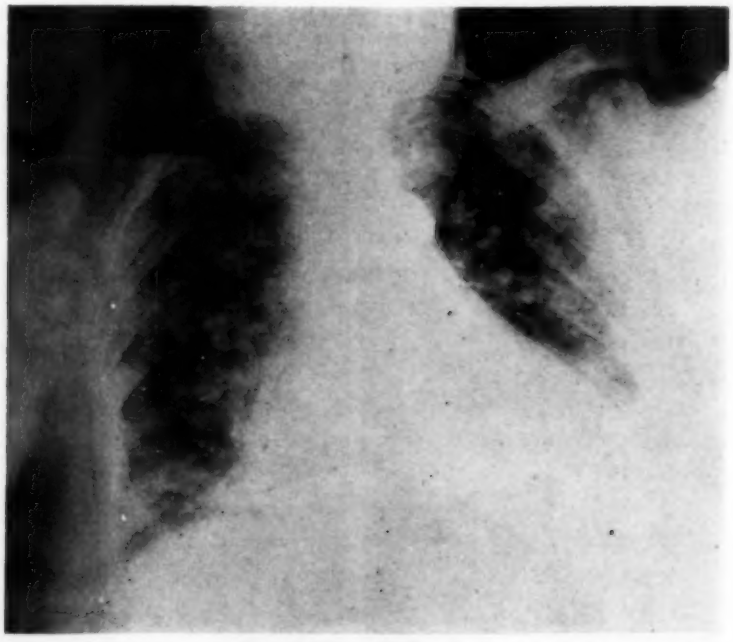

FIG. 5. Chest roentgenogram showing enlargement of heart and calcium deposits in lung fields.

DISCUSSION

In Paget's disease, tissues other than bone have been found to contain calcium deposits. Renal calculi are not uncommon, occurring in 10 per cent of Snapper's cases.[3] Then again, renal calculi are not infrequently found in bone lesions of many different etiologies.[4] Moehlig and Adler,[5] in a series of 26 cases of Paget's disease, found gall-stones in three of them. They found calcified adenomata of the thyroid gland in two patients and calcified fibroids in three of the 12 women in their series.

In the case of Wells and Holley,[1] besides the "metastatic" soft tissue calcification, supersaturation of the blood with calcium produced when carbon dioxide was lost through respiration caused calcium precipitation in the venous pulmonary circulation of the alveoli; the pulmonary arteries escaped but the small veins were heavily calcified. Often about the acid secreting glands of the stomach was found a dense ring of calcium deposition when the excretion of hydrochloric acid had left a compensatory degree of local alkalinity. In the kidney, where secretion of acid urine had also produced local alkalinity, there was a heavy microscopic deposit of calcium in the tubules and to a lesser degree in the arteries.

Our patient in 1935–1936 was given calcium and viosterol, an accepted form of therapy at that time. Roentgenograms taken just previous to this are unavailable to us and we are unable to state definitely whether calcification of the soft tissues existed at that time, but it was not so reported by a competent roentgenologist. When examined three years later, she showed extensive calcium deposits in both legs. These increased in amount from 1939 to her death in 1943. During the entire period of observation she had cardiac insufficiency with marked edema of both legs and feet. The veins of both lower extremities had been affected by phlebitis 11 years previously.

It is difficult to explain with the information at hand why calcification of the soft tissues of the body occurred in this case and in that described by Wells and Holley. In osteitis deformans a negative calcium and phosphorus balance is present in the earlier and more active form of the disease and a positive balance occurs in the later and less active stages with the blood calcium and phosphorus levels normal throughout.[6] The serum phosphatase, however, is markedly increased during the entire disease and sometimes so to extremely high levels.[7] When present, hypercalcemia (in an individual with skull signs of Paget's disease) means that we may be dealing with a coexisting hyperparathyroidism.[8] Albright [9] feels that the condition starts as a destruction of the bone which fits in with the findings of a negative calcium and phosphorus balance present earlier in the disease; osteoblastic stimulation due to increased stress and strain is the second step and results in overgrowth of bone and increase of serum phosphatase. In our patient, the phosphatase level was high in 1935.

London and Bernheim [10] administered 10 c.c. of 20 per cent calcium gluconate intravenously in 17 cases with unidentified stages of Paget's disease and found a lack of the normal expected elevation of the blood calcium. An increased affinity of the bones and other tissues for this calcium was their explanation. Moehlig and Adler [5] were unable to prove that feeding calcium phosphorus compounds or large doses of vitamin D improved the osteoporosis. On the contrary they feel that the giving of calcium is distinctly harmful as there is a tendency to increase calcium deposits in the soft tissue; then, too, viosterol may increase the arteriosclerosis which is so frequently present in Paget's disease. Vitamin D feeding had no appreciable effect on the calcium phosphorus balance in two cases described by Albright et al. In one of Sugarbaker's cases 10 years of treatment with vitamin D and calcium showed indifferent changes.

We want to stress, in these two cases, the absence of chronic renal insufficiency which can be associated with the protracted presence of calcium and phosphorus ions in the blood in concentrations far in excess of those at which deposition of calcium phosphate may be expected theoretically.[11] In the case of Wells and Holley the kidneys showed no gross evidence of renal damage at autopsy. In our case the blood phosphorus level was reported as elevated in 1939 but later that year it became normal. This would disprove any permanent renal damage. We are in no position to state whether or not renal or pulmonary calculi existed.

In our case edema and venous stasis due to heart failure were observed in both lower extremities for eight years. It should be noted that after her last Cæsarean section in 1924 she had a bilateral phlebitis. In an attempt to explain disseminated ossification of the lungs, Wells and Dunlap [12] claim that venous

stasis or general circulatory impairment favors bone production provided that other conditions conducive to ossification are present. Furthermore, they feel that in occasional cases a rise in CO_2 is responsible for an increase of calcium in the blood. Since the calcium deposits were not universal but were limited to the legs, we feel that the edema played an important rôle in its causation.

The therapy of Paget's disease is as obscure as is the etiology of the condition. However, Snapper still advocates the administration of calcium, phosphorus and ultraviolet rays in certain cases with osteomalacia: "The condition of the bone improves although the underlying osteitis deformans remains the same." In calcinosis, a ketogenic diet and disodium phosphate have been advised as well as a unilateral thyroidectomy and parathyroidectomy.[13] The latter has been carried out in osteitis deformans [14] but is not generally employed. Gill and Stein [15] suggest a low calcium and phosphorus diet supplemented with magnesium carbonate. The relation of protein, sex hormones,[16] and adrenal cortex [17] to bone metabolism has been stressed. Moehlig and Adler have found in Paget's disease a glucose tolerance curve which resembled that of a diabetic; they gave 15 units of insulin together with a constant weighed diet and found a disappearance of bone and head pains with an increase of strength.

No effective measures for the treatment of Paget's disease have yet been devised. However, certain facts have been established. Microscopically in this disease there is a tendency to the precipitation of calcium salts in the tissues.[18] The markedly increased phosphatase may have a close causal relation to the calcification.[19] Feeding of calcium phosphate or vitamin D may also promote the precipitation of calcium salts. The minerals and vitamin D used in our case, however, we believe were probably incidental rather than important factors in causing the deposition of calcium salts in the legs. It is interesting to note that the calcium deposits acted like foreign bodies, as evidenced by the granulomatous reaction in the case of Wells and Holley.

Summary

A second case of gross calcification of the soft tissue of the extremities occurring in Paget's disease is described. This was present in both legs which were edematous from cardiac failure. In a previous case of soft tissue and visceral calcium deposition the patient received viosterol. The calcium deposits acted as a foreign body in causing a granulomatous reaction. In our case, the patient received viosterol and calcium. We feel, however, that the giving of calcium and viosterol was only a coincidence in our case but see no indication for its use in the later stages of osteitis deformans. These cases emphasize the finding of calcium deposits in the later stages of Paget's disease when a positive calcium balance exists.

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PULMONARY ACTINOMYCOSIS DUE TO *ACTINOMYCES GRAMINIS**

By John P. Lynch, M.D., and Rebecca A. Holt, M.A., *Richmond, Virginia*

The term, actinomycosis, is now applied by Topley and Wilson [8] to two groups of diseases of man and animals in which Actinomyces-like organisms are encountered. In the first group, the proliferation of an anaerobic organism as *Actinomyces bovis* gives the appearance of colonies which have a ray structure in pus or tissues and often are described as "sulphur granules" or *Drusen*. In the second group are included all aerobic filamentous branching organisms which form a felted mycelium without any radial arrangement and without granule formation. Two type species are: *Actinomyces graminis* which is non-acid-fast and forms no granules in tissues; and *Actinomyces asteroides,* which is acid-fast and forms no granules in tissues.

Of human actinomycosis, in 60 per cent lesions occur in the face and neck,

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From the Department of Medicine, McGuire Clinic, St. Luke's Hospital, and the Department of Bacteriology and Parasitology, Medical College of Virginia, Richmond, Virginia.

in 20 per cent in the abdominal cavity, 15 per cent in the thorax, leaving 5 per cent involving the skin and other portions of the body.[4] The mortality of pulmonary actinomycosis varies from 70 per cent [7] to 95 per cent.[4] The mode of transmission is obscure in infections with both the aerobic and anaerobic Actinomyces. Schneider and Finucane [6] believe the organism enters the body through a cavity in a tooth or through an open wound. Diagnosis is best made by microscopical and cultural examinations of the affected tissues. Prophylactic measures should be taken against the discharge from all lesions. No satisfactory methods of treatment can be recommended.

Interest in the presence in tissue of the aerobic, non-acid-fast Actinomyces, *Actinomyces graminis,* has been stimulated during the past decade, although it had been isolated from cases of human actinomycosis in 1891 by Bostroem.[3] In 1934 Biggart [1] reported the finding of *Actinomyces graminis* in a fatal case of generalized actinomycosis in a woman with the primary abscess in the left lung and secondary involvement of both lungs and liver, spleen, kidneys, and subcutaneous tissue of the left thigh and right arm. Zeitlin and Lichenstein [9] in 1937 described a case of actinomycotic abscess of the brain secondary to a small focus in the lung from which an aerobic Actinomyces was cultivated, although they failed to state whether or not this organism possessed acid-fast properties. Holt [5] in 1941 cultivated *Actinomyces graminis* from the pus of a brain abscess in the left parietal lobe of a woman 36 days prior to death. Permission for an autopsy was not granted and it could not be ascertained whether the lesion was primary or secondary. A low grade pathogenicity of this Actinomyces was demonstrated for rabbits and pathologic lesions similar to those in man were produced.

The pertinent clinical, bacteriological and pathological data of a case of pulmonary actinomycosis is presented in which *Actinomyces graminis* (Bostroem) was identified in bronchial secretion, sputa, and pleural fluid before death, and in pleural fluid and multiple abscesses of the lung on postmortem examination.

Case Report

J. E. F.,* a 16 year old high school boy, was quite well until September 22, 1943, when he was taken with pain in the left chest anteriorly, headache, general malaise, temperature of 102° F., and a nonproductive cough. There was stiffness of his joints but no swelling or tenderness.

He was first seen by me (J. P. L.) and admitted to St. Luke's Hospital on October 29, 1943, when he volunteered the following additional information. He had had night sweats during the preceding week, and dyspnea and precordial pain. His mother had noticed nervousness and poor color since the onset. There were no other systemic symptoms of significance, except a weight loss of 30 pounds.

Past history revealed he had measles, mumps, varicella, and pertussis in childhood. There was no history of pneumonia or asthma, or surgical operation. The family history was negative except that his mother had had a thyroidectomy before his birth. There was no family history of tuberculosis. He was a native of Virginia, lived in the suburbs of Richmond, and was active in athletics, having frequently played football in open fields.

Physical examination revealed the following significant findings: Height 5 feet, 9½ inches, weight 128½ pounds, temperature 101.7° F., and pulse 108. He was a

* We wish to acknowledge our indebtedness to Dr. M. J. Page who referred this case.

well developed, but poorly nourished boy who had a notable pallor. His sinuses transilluminated poorly and there was a postnasal mucoid discharge. The cervical, axillary and inguinal glands were not enlarged. There was an area of dullness on percussion at the left base posteriorly extending for two or three inches above the level of the diaphragm, and an area of cardiac dullness extending 12.5 cm. to the left of the midsternal line. No râles were heard, but the breath sounds in these areas were diminished or absent. The heart sounds were of fairly good quality. There was a soft systolic murmur in the pulmonic area. The blood pressure was 100 mm. Hg systolic and 60 mm. diastolic. The liver and spleen were not palpable. The genitalia, reflexes, and extremities were normal.

Examination of the chest two days later revealed dullness at the left lung apex anteriorly extending down the whole anterior surface of the left chest.

Laboratory examinations on admission were as follows: Blood: Hemoglobin, 67 per cent (Sahli); white cell count, 15,400, with 85 per cent neutrophiles, 12 per cent lymphocytes, 1 per cent mononuclears, and 2 per cent eosinophiles. Urine: Amber, cloudy, specific gravity 1.026, acid, faint trace of albumin, no sugar and no acetone; rare red blood cell, one to two pus cells per high power field, large amounts of mucus, and many crystals (sulfadiazine). Sputum: Bloody with numerous Gram positive filaments, but no acid fast bacilli or filaments. Agglutination tests with antigens of *E. typhosus* ('O' and 'H' antigens), *B. paratyphosus, Proteus* X 19, *Br. abortus, P. tularensis* were all negative. Six blood cultures were negative. An electrocardiogram was normal in all four leads.

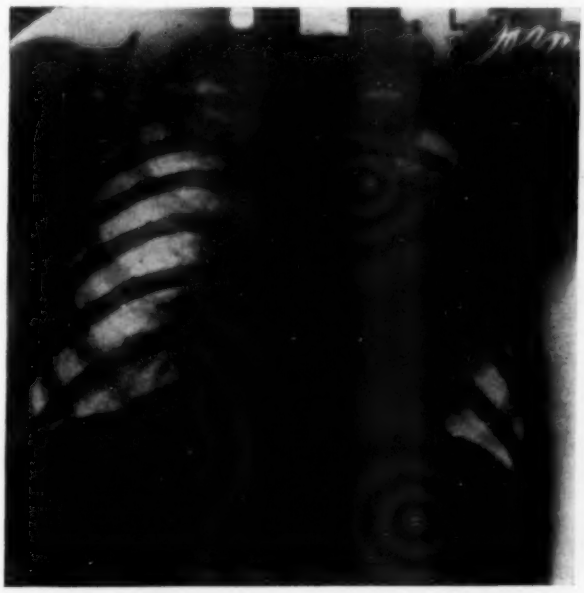

FIG. 1. Flat plate of chest made October 29, 1943.

On October 29, Dr. J. L. Tabb of the McGuire Clinic made a roentgenogram of his chest and reported that "appearances indicate an atypical pneumonia extending outward from the root of the left lung practically to the periphery" (figure 1).

Prior to admission to the hospital, a total of 15 grams of sulfadiazine over a 10 day period was administered. On November 3, he was given 2 grams sulfamerazine, 2 grams four hours later, and then one gram every eight hours for five days, day and

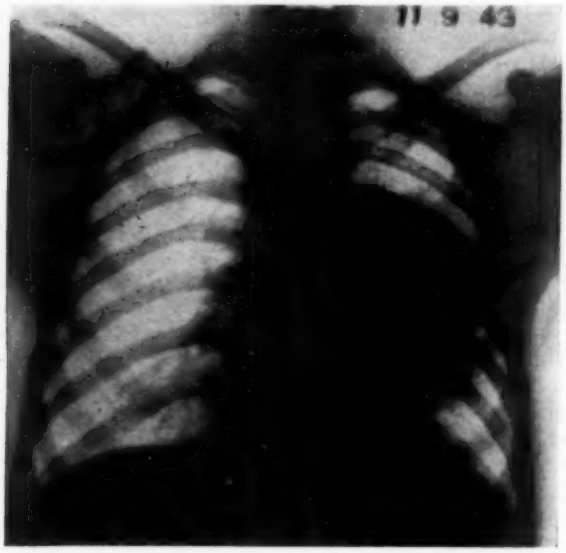

FIG. 2. Flat plate of chest made November 9, 1943.

night. There was no appreciable effect on the temperature which averaged 101° F.

Chest roentgenogram on November 9 showed a spread of the pneumonic process in the left lung and three rarefied areas resembling cavities were noted in this process (figure 2).

On November 10, Dr. Porter Vinson of the Medical College of Virginia, made a bronchoscopic examination of the patient. An inflammatory lesion causing partial obstruction of the left upper lobe bronchus was reported. Material obtained during bronchoscopy revealed the presence of numerous Gram positive filaments resembling morphologically actinomyces (figure 3) and many yeast-like organisms resembling

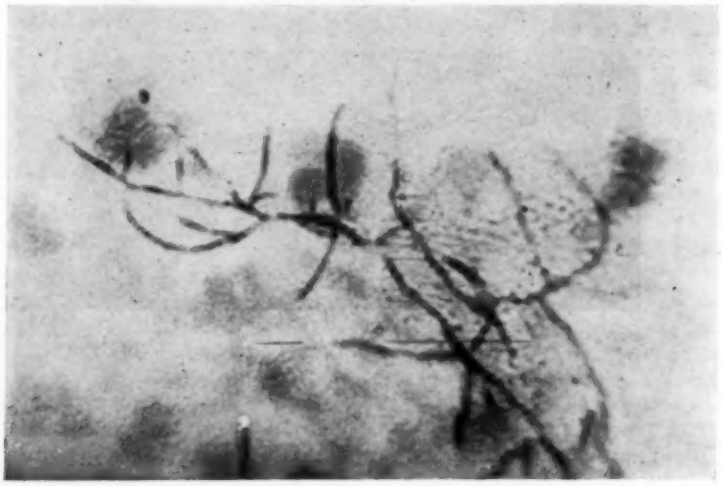

FIG. 3. Smear preparation of *Actinomyces graminis* in bronchial secretion. Gram's stain. (×1440.)

monilia. No acid fast bacilli or filaments were demonstrated on direct microscopic examinations. Cultures were not made on this specimen. On three subsequent specimens of sputa, *Actinomyces graminis* was identified by cultural means, although *Monilia albicans* was found in only one of these specimens. Studies of *Actinomyces graminis* isolated from sputum were also made after intravenous and intraperitoneal inoculations into white mice. Within two weeks after injections, the mice were either sacrificed or died. Actinomyces were seen in the multiple abscesses formed in the liver, spleen, lung and kidneys, when studied in direct smears and in sections stained by Gram's method. No "sulphur granules" or Drusen were formed in the tissues. The characteristic picture seen was the presence of irregularly stained, Gram positive, branching filaments in granulomatous tissue with multiple abscess formation and necrosis. At no time were acid fast filaments or bacilli found.

Actinomyces graminis as isolated from this case possessed the following characteristics: *Morphology:* Irregularly staining, branching filaments (figure 3). No terminal granules. *Tinctorial properties:* Gram positive. Non-acid-fast in young and old cultures and in tissue, sputum and pleural fluids. *Motility:* Non-motile. *Biological properties:* Grew readily on ordinary culture media and on media for fungi at room temperature and at 37° C. in 24 to 48 hours. Aerobe. Failed to grow anaerobically in chopped meat and Brewer's media.

Semi-solid dextrose brain infusion agar. Abundant surface growth in 24–48 hours at 37° C. Early growth was white and feathery. It gradually deepened in color from cream to orange to brown and became more firm and adherent. Surface growth might show definite colony formation or it might be a dull, finely granular or mealy pellicle.

Blood agar. Aerobically within 24 hours at 37° C., definite chalky white, feathery, surface colonies developed which varied in size from pin point to pin head. Colonies increased in size in 48 to 72 hours. Appearance changed as center changed from cream to yellow to brown and became more granular. Periphery increased its feathery or rhizoid arrangement. Generally firm and adherent to solid media. Difficult to emulsify.

Corn meal agar and Sabouraud's dextrose agar. Growth at 20° C. essentially the same as that on blood agar at 37° C.

Dextrose broth. Early colony formation resembled balls of cotton (figure 4) on surface of broth. Older growths deepened in color. Failed to ferment dextrose.

Loeffler's blood serum. No liquefaction. Typical colony growth. White feathery periphery with cream to orange to brown centers.

Gelatin. No liquefaction. Abundant typical surface growth. Growth decreased along stab.

Milk: Slightly alkaline. Typical surface growth.

Chopped meat. No growth.

Brewer's medium. Aerobic growth abundant. No anaerobic growth.

Carbohydrate semi-solid infusion agar. No fermentation during four weeks of dextrose, lactose, saccharose, maltose, mannite, xylose, dulcite, dextrin, sorbitol, levulose, arabinose, or inosite. Surface growth abundant. Colonies showed cream-orange pigmented centers with effuse white feathery edges. Adherent to media.

Beginning November 13 the patient received daily roentgen-ray therapy totalling 800 r. to the left anterior chest and 400 r. to the posterior aspect (220 KV with thoracic filter used). Twenty-four hours after the first roentgen-ray treatment, the temperature rose from a level of 101° to 103° F. In addition to the radiation, he was given 15 grains of sodium iodide by vein daily and saturated solution potassium

iodide 21 drops three times daily, increasing by one drop three times daily until his discharge from the hospital when he was receiving 35 drops three times a day. On November 26, he received 500 c.c. blood by vacuum flask citrated method without reaction.

His course at home was progressively downward. He suffered drenching sweats, increasing dyspnea with a respiratory rate of 36 per minute and a wracking cough. His appetite gradually failed and he became too weak to sit up. On December 11 a loud pericardial friction rub was heard. A punctate maculopapular rash appeared over his abdomen and legs, which was thought to be an iodide skin reaction. He was getting 50 drops saturated solution potassium iodide three times daily, and the drug was temporarily discontinued. Intradermal injections of both *Monilia albicans* and *Actinomyces graminis,* isolated from the sputum, produced little or no cutaneous reaction 48 hours later.

FIG. 4. Surface colony of *Actinomyces graminis* in dextrose broth after aerobic cultivation for 72 hours at 37° C. (× 12.)

The antigens used for the skin testing were a suspension of the growth of 72 hour cultures in physiological normal salt solution, standardized to MacFarland's nephalometer No. 3 and autoclaved for 15 minutes at 15 pounds pressure. Liquid phenol was added in 0.5 per cent concentration. An attempt to immunize the patient with a vaccine was not thought advisable.

On December 16 he was readmitted to St. Luke's Hospital. His temperature was 101° F., pulse 160, and respirations 32. His eyes had a glassy appearance. The entire left chest was flat on percussion both anteriorly and posteriorly. Moist râles were heard throughout. The pericardial rub had disappeared, but the heart tones were of poor quality. Blood pressure was 90 mm. Hg systolic and 70 mm. diastolic. There was moderate abdominal distention. The hemoglobin was 64 per cent (Sahli), the white count 44,900 cells per cubic millimeter with 93 per cent neutrophiles and 7 per cent lymphocytes. The total count on the day of death was 70,000 cells per cubic millimeter with 91 per cent neutrophiles. The urine was acid and showed a faint trace of albumin, but was otherwise negative.

The electrocardiogram showed ST elevation in the three standard leads, consistent with changes noted in acute pericarditis. The roentgenogram showed complete homogeneous opacity of the left lung and bronchial thickening of the right.

On December 17, 500 c.c. of cloudy, straw colored fluid were removed from the left pleural cavity. A culture of this fluid showed the presence of *Actinomyces graminis*. Neither acid fast bacilli or filaments nor monilia could be demonstrated.

During the last 48 hours of his illness, he received 100,000 units of penicillin with no apparent benefit and died quietly December 17.

Autopsy: Actinomycosis of the left upper lobe of the lung with invasion of the pericardium, subacute adhesive pericarditis, chronic myocarditis (figure 5), and left empyema as well as an acute splenic tumor and chronic passive congestion of the liver were reported by Dr. J. H. Scherer. Sections of the lung stained with hematoxylin and eosin showed chronic granulation tissue with multiple foci of abscess formation and necrosis. Bacteriological stains of the sections of the lung and pericardium with

FIG. 5. Lung-heart gross specimen showing multiple actinomycotic abscesses (at right) with direct extension into pericardium.

Gram-Weigert stain revealed numbers of the branching actinomyces (figure 6). The presence of *Actinomyces graminis* in the pleural fluid collected at the time of autopsy was again demonstrated by cultural means, although no monilia were found. Cultures of the abdominal fluid taken at autopsy proved negative for both actinomyces and monilia. No acid-fast bacilli or filaments were seen in direct smears of the sediments of either the pleural or abdominal fluids collected after death.

SUMMARY

1. An actinomycosis infection, probably primary in the lung, of a previously healthy 16 year old boy is reported.

2. Treatment with sulfadiazine, sulfamerazine, roentgen-ray radiation, iodides and blood transfusion was ineffectual.

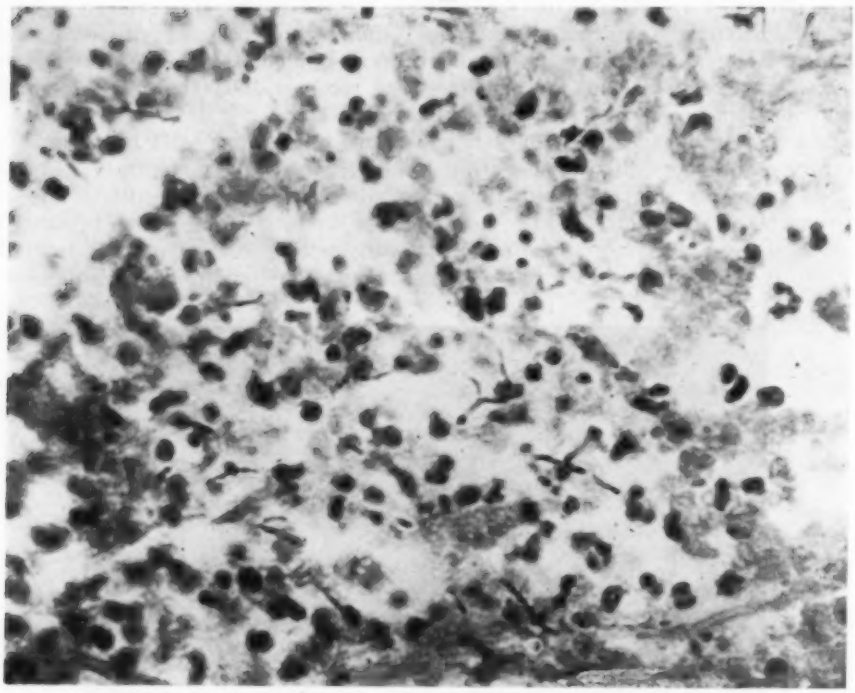

FIG. 6. Section of human lung showing branching filaments of *Actinomyces graminis* distributed throughout the chronic granulation tissue without any radial arrangement and without any formation of granules or *Drusen*. Gram-Weigert stain. (×720.)

3. From the onset of symptoms to death, the duration was 85 days.

4. *Actinomyces graminis* was identified by bacteriological means in the bronchial secretion, sputa and pleural fluid prior to death and in pleural fluid after death.

5. Postmortem gross studies revealed actinomycosis of the left upper lobe of the lung with direct extension into the pericardium giving rise to a subacute adhesive pericarditis, chronic myocarditis, and empyema on the left side. Gram positive branching filaments of *Actinomyces graminis* were distributed throughout the tissue. No radial arrangement or granule formation (*Drusen*) was observed.

6. A low grade pathogenicity for white mice was shown by the *Actinomyces graminis* isolated. Bacteriological and pathological findings were the same as seen in the studies of man.

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MECHANISM OF REFLEX ANURIA *

By George A. Wolf, Jr., M.D., *New York, N. Y.*

Although in urologic literature a syndrome of so-called reflex anuria has been recognized, its explanation has never been satisfactory. Kasten,[1] in classifying the anurias, includes an inhibitory form of reflex anuria said to be the result of a fall in blood pressure below the critical level necessary for glomerular filtration. He states that such anurias may accompany a fall in renal blood pressure following splanchnic stimulation in abdominal operations. Another more common cause of reflex anuria is said to be the decreased glomerular filtration pressure resulting from a fall in systemic blood pressure associated with shock from painful injuries or prostrating illnesses. Moon,[2] however, points out that a fall in systemic blood pressure is not a constant accompaniment of renal shut down and cites instances following crush injuries in which diminished renal output persisted after the blood pressure had returned to normal. To explain such occurrences a noxious substance produced by the damaged tissues of patients with crush injuries has been postulated as a factor concerned in the diminution of renal function.

Hipsley [3] came to the conclusion that all of the cases of reflex anuria which he could discover in one hospital might be explained on the basis of calculous obstruction of the urinary tract which had not been clinically evident at the time the diagnosis of reflex anuria was made. Elward [4] has reported a case in which transient unilateral suppression of renal function was unassociated with shock, with changes in blood pressure, or with organic obstruction to the urinary tract. Adler [5] has described a patient in whom anuria appeared to be related to emotional factors and was relieved by hypnosis.

Study of the following case casts some light upon mechanisms which may be involved in reflex anuria.

Case Report

The patient was a 32 year old male who considered himself well until approximately one year before his entry into the hospital, at which time he began to suffer from headaches. Two weeks before admission the patient noted the onset of gross

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From the Department of Medicine, Cornell University Medical College and New York Hospital, New York City.

hematuria and occasional sharp right flank pain which persisted until the time of admission. He was found to have a blood pressure of 230 mm. Hg systolic and 108 mm. diastolic. The urinary output for the eight hours prior to cystoscopy was 600 c.c. Cystoscopy was performed without local or general anesthesia. Grossly bloody urine was observed coming from the right ureter and no phenolsulfonphthalein was excreted from either kidney in 10 minutes. Bilateral retrograde studies were completed and found to be normal. The patient did not void following cystoscopy until the next day when, in spite of a 3000 c.c. intake, only 100 c.c. of bloody urine were excreted. The blood pressure was 160 mm. Hg systolic and 110 mm. diastolic. Fifty per cent glucose and theocalcin were given repeatedly. The urinary output averaged 200 c.c. a day in spite of an intake of over 2000 c.c. a day for five days. The patient was seen eight days after cystoscopy by a consultant who made the following observations. The temperature was 38.2° C.; the pulse was 100 per minute; the respirations were Cheyne Stokes in type; and the blood pressure was 170 mm. Hg systolic and 100 mm. diastolic. The patient was in a semidelirious state. The eye grounds revealed evidence of arteriolar disease with hemorrhage and exudate. The mucous membranes were dry and the breath was uriniferous. The lungs were found on auscultation to contain many moist râles at both bases. The heart was enlarged to the left and the rate was rapid but regular. There was a loud to and fro precordial friction rub. The venous pressure was estimated to be 200 mm. of water. The liver was just palpable, and there was no edema.

The urine examination showed a specific gravity of 1.012, two plus albumin, many red blood cells but no casts. There was a moderate anemia and a leukocytosis of 40,000. The blood urea nitrogen had risen from 57 to 193 milligrams per cent. The carbon dioxide combining power was 34 volumes per cent. The serum proteins were 6.1 grams per cent. The serum phosphorus was 10.4 milligrams per cent and the serum calcium was 9.3 milligrams per cent. Intravenous injection of phenolsulfonphthalein resulted in the excretion of no detectable dye in two hours. At this time the patient was no longer anuric but was excreting an average of 1000 c.c. of urine a day. During the following week his condition became progressively worse and resulted in his death from uremia on the fifteenth day following cystoscopy. Postmortem examination of the kidneys revealed a diffuse pyelonephritis with multiple small abscesses throughout both kidneys. The renal arterioles showed rather marked thickening and hyalinization of the medial coat. The tubules showed blockage by leukocytes and precipitated protein. The glomeruli were unremarkable.

Discussion

Wolf [6] has shown that in normal individuals the application of a painful stimulus to the head by means of a pressure device may result in suppression of urine flow. By means of diodrast and inulin clearances this effect could be attributed specifically to a decrease in renal blood flow which was not associated with a fall in systemic blood pressure. The blood pressure rose during the application of the painful stimulus even though the subject developed cold, moist extremities and became pale and nauseated. It was further shown that the decrease in the rate of glomerular filtration was relatively small when contrasted with the diminution in renal blood flow. Although it was pointed out that the response of the kidneys to pain resembled that seen following the injection of adrenalin (Chasis, et. al.[7]), it was not postulated that the change in renal blood flow was an adrenalin effect. Rydin and Verney [8] have demonstrated that in dogs the oliguria associated with a "startle" reaction is not dependent upon the innervation of the kidneys or the presence of the adrenal glands. They postulate

that the antidiuretic hormone of the neural lobe of the hypophysis is responsible for the oliguria observed in their experiments. However, ignorance of the neural and humoral control of the kidney makes it impossible to speculate upon the intermediary mechanisms of the reaction of the kidney to noxious stimuli. Pain or the reaction of the individual to pain may alter the functional state of the kidney without a coincident fall in systemic blood pressure.

The question arises whether the alteration in the functional state of the kidney associated with painful stimuli may become permanent under certain conditions. Corcoran and Page [9] have observed that prolonged decrease in renal blood flow resulting from hypotension due to bleeding in dogs decreases the ability of the kidneys to respond to restoration of blood pressure. The facts that thrombi are found in the glomerular tufts in chronic glomerular nephritis, that there is a reduction in the arteriolar lumen in vascular disease of the kidney, that coagulated protein is found in the tubules of patients with "crush syndrome," and that thrombi are found in the cortical arterioles of patients with bilateral cortical necrosis (Duff and More [10]) suggest that in the presence of any of these lesions marked reduction in renal blood flow would seriously affect kidney function and produce irreversible structural changes in the kidney with subsequent renal failure.

It is suggested, therefore, that the reflex anuria following cystoscopy in the case reported in this paper reflected a marked diminution in the patient's renal blood flow. It would appear that the changes induced lead to the rapid onset of renal decompensation. This patient's course further suggests that in the presence of advanced renal disease, diagnostic or therapeutic procedures which present a noxious stimulus with pain and which might cause reflex anuria should be avoided.

Summary

1. A case of reflex anuria following cystoscopy is presented.

2. The patient had preëxisting renal disease. Following the episode of reflex anuria he developed renal decompensation and died.

3. It is pointed out that pain may cause a reduction in renal blood flow and that reduced renal blood flow may cause irreversible changes in the previously damaged kidney.

4. It is suggested that painful or shocking procedures on patients with marked kidney damage should be approached with care.

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DEXTROCARDIA WITH SITUS INVERSUS COMPLICATED BY CHRONIC RHEUMATIC AORTIC AND MITRAL ENDOCARDITIS *

By George W. Parson, M.D., F.A.C.P., *Texarkana, Arkansas–Texas*

Congenital dextrocardia with situs inversus is a relatively uncommon anomaly. LeWald [1] recorded an incidence of one in 35,000 physical examinations of recruits for the United States Army. We have recognized two in approximately 15,000 private patients. Dextrocardia complicated by acquired organic heart disease must be rare. No careful search of the literature has been made but a recent paper,[2] in which a case of dextrocardia complicated by calcareous aortic stenosis was described, listed only five former case reports. In these the acquired lesions were mitral stenosis,[3] hypertensive heart disease,[4] coronary thrombosis,[5] hypertensive and coronary heart disease,[6] and syphilitic aortitis and aortic insufficiency.[7] A patient with dextrocardia and coronary artery disease was reported by Crawford [8] in 1939. In the same year, Konar [9] described a case of congestive cardiac failure due to emphysema in a patient with generalized transposition of viscera. Autopsy findings were given, but no electrocardiographic data were presented. Apparently no case of dextrocardia complicated by combined aortic and mitral endocarditis has been recorded. The following report should be of interest.

Case Report

Mrs. I. A. C., a 24 year old white housewife, was referred to us September 14, 1942 because of heart disease. Dextrocardia had been recognized at the age of one month. Infancy, childhood, and young adult life had been perfectly normal. The usual activities, including basketball, caused no abnormal symptoms. In December, 1939 at the age of 21 years, the patient had an acute illness characterized by fever and red, swollen, painful joints. She recovered in five weeks without any known cardiac complications. The patient was married at the age of 18 years and had two children, three and one-half years and 14 months old. The first pregnancy was uneventful. During the second a cardiac lesion was recognized, but apparently no myocardial failure developed. In September, 1941, approximately two months postpartum the patient was put to bed with sore throat, fever and dyspnea. She improved, but influenza necessitated bed rest again late in 1941 and she was not well after that. Although she was out of bed from time to time, dyspnea was always troublesome. A few weeks before our examination the ankles were swollen and they were sore enough to interfere with walking, and five weeks prior to our studies, she was hospitalized

* Received for publication February 18, 1944.

because of orthopnea and edema. Improvement occurred on digitalis and intravenous diuretics. When we saw the patient the chief symptoms were pain in the right side of the thorax and "throbbing of the heart." She was receiving digitalis but the amount was not recorded.

One maternal uncle died of hypertension. Otherwise the family history was unimportant.

On physical examination the patient was comfortable at rest. She appeared weak and chronically ill. Blood pressure was 95 to 105 mm. Hg systolic and 50 mm. diastolic. Temperature was normal. The heart rate was 110 per minute, and on first examination there was a short period of coupled rhythm. This was not noted again.

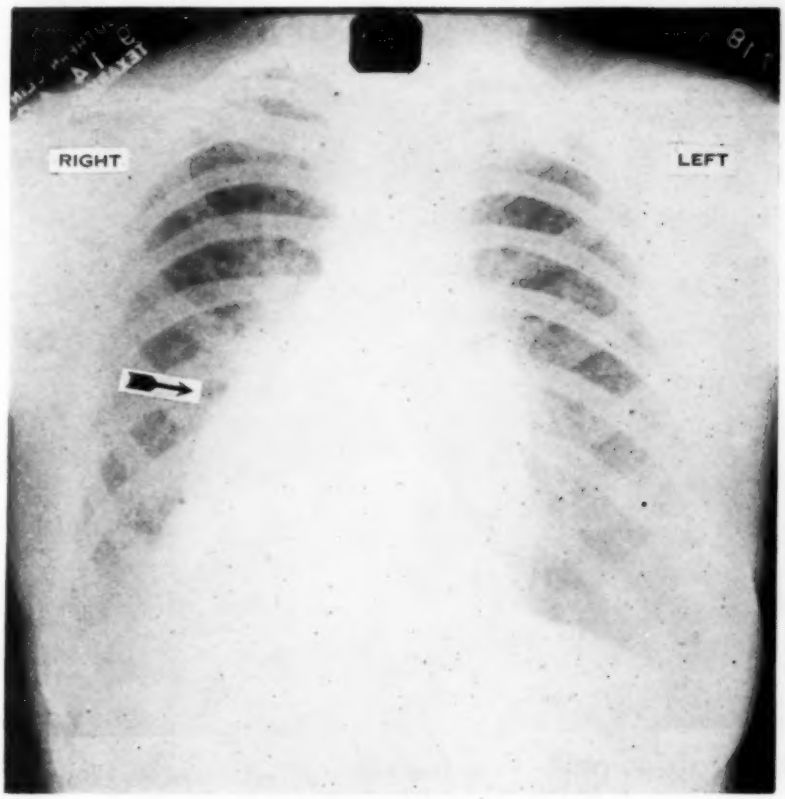

FIG. 1. Anterior View: Dextrocardia, moderate cardiac enlargement, marked enlargement conus area (black arrow) right ventricle, small right sided aortic knob, increased lung markings, increase in size of hilar shadows, left leaf of diaphragm higher than right.

The cardiac apex impulse was visible and palpable well outside the mid-clavicular line, 11 cm. to the right of the mid-sternal line. There was a pronounced systolic thrill at the base of the heart. On auscultation a loud harsh systolic aortic murmur, well transmitted to the neck, and a distinct diastolic aortic murmur were present. The first mitral sound was loud and crescendo. There was a slight systolic and a distinct diastolic murmur at the mitral area. The diastolic murmur was indistinguishable from the one heard at and below the aortic area. A few crepitant râles were present at the lung bases. The liver was palpable in the upper left abdomen. There was no

pitting edema, but the tissues over the sacrum and hips were puffy. Physical examination was otherwise not remarkable.

A specimen of urine was negative except for an occasional pus and red blood cell. The leukocyte count was 12,100. The blood count was otherwise normal. Blood urea was 20 mg. per 100 c.c. of blood and the blood Kahn reaction was negative. The sedimentation rate was not determined.

Fluoroscopic and roentgenologic examination of the chest (figures 1 and 2) re-

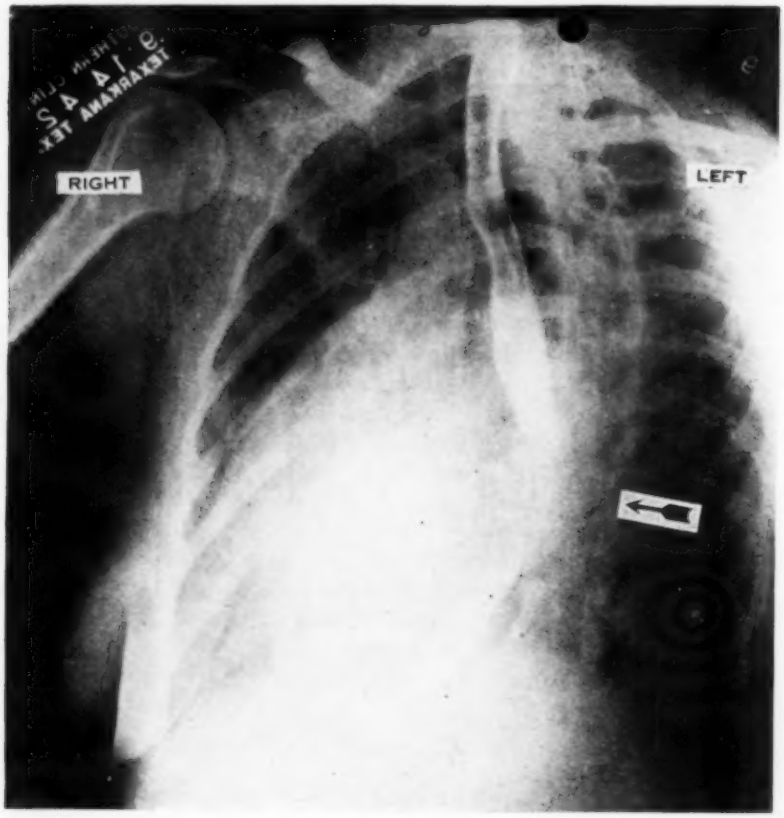

FIG. 2. Left Anterior Oblique View: Displacement dorsally of barium filled esophagus by enlarged left auricle (black arrow).

vealed in the anterior view transposition of the heart, moderate cardiac enlargement, small right-sided aortic knob, marked enlargement of the conus (black arrow) of the right ventricle, increased markings in the lung fields and enlarged hilar shadows. The left leaf of the diaphragm was higher than the right. In the left oblique view the important finding was dorsal displacement of the barium filled esophagus by an enlarged left auricle (black arrow, figure 2).

Transposition of the stomach and colon was demonstrated by fluoroscopic and roentgenographic examination following a barium meal.

Electrocardiographic examination * (figure 3a): Sinus rhythm, ventricular rate

* These tracings were made October 25, 1942. Those taken September 14, 1942 were not satisfactory for reproduction.

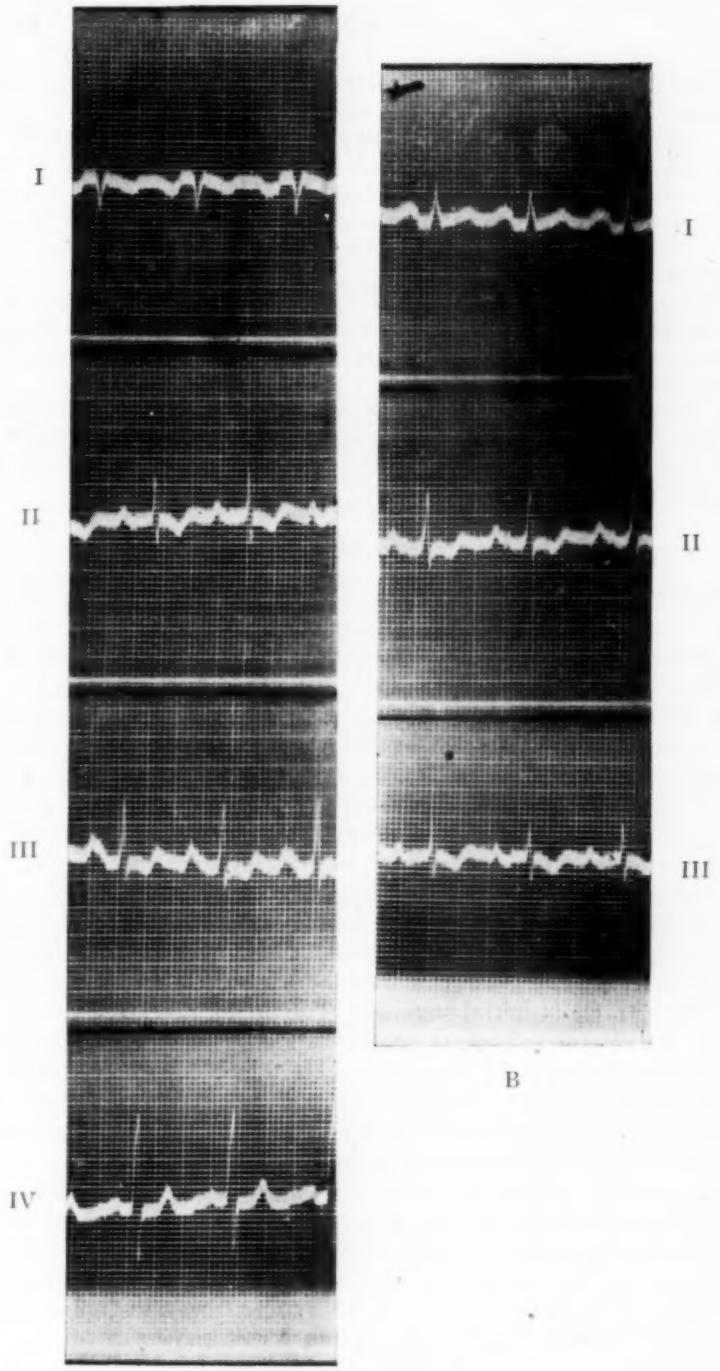

FIG. 3. A. Leads I, II, III, and IV showing prolonged P–R interval, inversion of all complexes in Lead I, broad notched P-waves in Leads I and III (transposed II), small S-waves in Lead II (transposed III) and smaller S-waves in Lead III, inverted T-wave in Lead II and diphasic T-waves in Lead III. B. Electrodes reversed in limb leads to correct for the dextrocardia: Note especially slight left axis deviation, broad P-waves particularly in Lead I and diphasic T-waves in Leads II and III.

92, right axis deviation, P–R interval 0.22 second and QRS interval 0.08 second. Lead I revealed the characteristic features of congenital dextrocardia, i.e., inversion of P-, QRS- and T-waves, and in addition broad (0.13 sec.) notched P-waves. In Lead II (transposed Lead III) there were small (3 mm.) S-waves, normal P-waves, and inverted T-waves. Lead III (transposed Lead II) showed upright, broad (0.12 sec.), notched P-waves, small (2 mm.) S-waves, and diphasic T-waves. Lead IV was normal. In tracings (figure 3b) made with the arm wires reversed to "correct" for the dextrocardia the significant changes were the broad, notched P-waves in Leads I and II, the small (2 mm.) S-waves, and the diphasic T-waves in Lead II, and the larger (3 mm.) S-waves and diphasic (or inverted) T-waves in Lead III. There was a slight left axis deviation instead of a right axis deviation. Prolongation of the P–R interval persisted.

The patient was returned to her home physician, Dr. H. G. Heller, Hope, Ark., for treatment. She was not seen again except for a few minutes October 25 when the electrocardiograms reproduced here were made. Improvement was temporary and death occurred November 30, 1942.

Discussion

The history and physical findings, the demonstration of the location and configuration of some of the thoracic and abdominal organs by roentgenology, and the changes recorded by electrocardiography were diagnostic of dextrocardia with situs inversus.

There was adequate evidence for the diagnosis of chronic rheumatic aortic and mitral endocarditis. The history of an acute febrile illness resembling rheumatic fever was obtained. The physical findings of a pronounced systolic basal thrill and a loud well transmitted systolic and a distinct diastolic aortic murmur in a young person are diagnostic of chronic rheumatic aortic endocarditis. The characteristics of the first mitral sound and the systolic and diastolic murmurs heard at the cardiac apex were most suggestive of chronic mitral endocarditis in spite of the fact that the aortic manifestations were predominant. The fluoroscopic and roentgenographic findings of enlargement of the conus area of the right ventricle and of enlargement of the left auricle are the usual structural changes demonstrable in mitral stenosis. The broad, notched P-waves in Leads I and II of the electrocardiogram are indicative of left auricular strain and the T-wave changes in Leads II and III suggest right ventricular strain. Both of these are produced by mitral stenosis. The very slight left axis deviation instead of right deviation suggests that there was a predominant left ventricular strain such as is found in aortic lesions.

The prolonged P–R intervals present in the tracings taken on both September 14 and October 25, 1942 could be indicative of myocardial disease.—There had been symptoms suggestive of recurrence of rheumatic fever a few weeks before our examination.—The patient had been taking one cat unit of digitalis daily for approximately six weeks at the time of the last electrocardiographic examination. The dose at the time of the first cardiogram is not known.

The electrocardiograms were interesting and instructive. They revealed:

1. Findings diagnostic of dextrocardia. (Inversion of all complexes in Lead I.)
2. Evidence of left auricular strain. (Broad notched P-waves in Leads I and II.)

3. Evidence of right ventricular strain. (Inverted T-waves in Lead III and diphasic T-waves in Lead II.)

4. Questionable evidence of left ventricular strain. (Very slight left axis deviation.)

5. Evidence of myocardial damage. (Prolonged P–R interval.) This may have been due to digitalis but it was present on two occasions six weeks apart.

Summary

A case of congenital dextrocardia with situs inversus complicated by chronic rheumatic aortic (stenosis and regurgitation) and mitral (stenosis and probably regurgitation) endocarditis is presented. Roentgenographic and electrocardiographic findings are important and they can be correlated with the history and physical findings. No record of a similar case has been found.

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Erratum. In the article on "Demonstration of Visceral Pain by Determination of Skin Potentials" by Drs. Morrison and Spiegel, June Annals, page 831, the first paragraph under the Summary should read as follows: "1. The study of skin potentials is an objective method useful in the evaluation of visceral pain. In 74 per cent of the 31 cases with pain accompanying proved organic visceral disease, there was an increase of the skin potentials in the respective dermatomes over the remainder of the body by 10 or more millivolts."

EDITORIAL

LUMBODORSAL SYMPATHECTOMY FOR HYPERTENSION

Operations on the sympathetic nervous system designed to relieve hypertension have aroused considerable interest for a number of years. Results from the majority of the earlier procedures were so variable that many surgeons and physicians became skeptical as to the possibilities inherent in this form of therapy. It is only in the past seven years that the more radical lumbodorsal sympathectomy developed by Dr. Reginald Smithwick has shown sufficiently good results to revive enthusiasm over the surgical treatment of hypertension.

The technic for the perfected operative procedure was published in 1940.[1] The purpose of the operation is to interrupt the vasomotor supply to the arterioles of the abdominal viscera. The two stages of the operation are performed about 10 days apart. The great splanchnic nerves are removed from the iliac ganglia to the midthoracic level and the sympathetic trunks are excised from at least the ninth dorsal to the first lumbar to at most the sixth dorsal to the third lumbar, inclusive. The operative mortality in Smithwick's hands has been less than 3 per cent in a series of over 500 cases, an unusually low rate considering the severity of the hypertensive disease in many of the patients.

Smithwick [2] noted that a significant and persistent lowering of the diastolic pressure followed operations of this order of magnitude in the majority of patients. This was associated with favorable changes in the eyegrounds, electrocardiograms, and cardiac and renal functions as well as in symptoms. The lowering of blood pressure was thought to be due to a decrease in the tone of arteriolar smooth muscle. Renal biopsies [3] from 100 hypertensive patients in the course of sympathectomy revealed no renal vascular disease or insignificant changes in 28 per cent and only mild changes in an additional 25 per cent. From these observations, it was concluded that the morphologic evidence of renal vascular disease in more than half the cases was inadequate to be regarded as the sole factor in producing the hypertension and that the hypertensive state antedated the renal vascular lesion.

On the whole, the results of the operation have been better in women than in men. Also, the results vary according to the type of hypertension with particular emphasis placed upon the width of the pulse pressure. Smithwick divided his patients into three types: narrow, intermediate, and wide pulse pressure, designated as Types 1, 2 and 3, respectively. In general,

[1] Smithwick, R. H.: A technique for splanchnic resection for hypertension, Surgery, 1940, i, 1–8.

[2] Smithwick, R. H.: Surgical treatment of hypertension, Arch. Surg., 1944, xlix, 180–192.

[3] Castleman, B., and Smithwick, R. H.: The relation of vascular disease to the hypertensive state, Jr. Am. Med. Assoc., 1943, cxxi, 1256–1261.

it was found that the wider the pulse pressure, the higher the percentage of poor results.

In order to answer the contention that the fall in pressure following sympathectomy might be merely a non-specific effect of a major surgical procedure, Rojas, Smithwick, and White [4] followed the blood pressures in a group of 100 hypertensive patients who underwent nonspecific major operations in order to compare these with a group of 100 patients who had had lumbodorsal sympathectomy. This study showed very convincingly that nonspecific major operations produce some immediate reduction in blood pressure of hypertensive patients, but that this reduction is not great and in the majority of cases persists for only a short time in contrast to the pronounced and lasting reduction in the majority of the sympathectomized cases. The specificity of lumbodorsal sympathectomy was also demonstrated by the fact that definite results were not observed until after the second stage operation had been performed, the first stage producing only about the same effect as any other major operation.

Granting that lumbodorsal sympathectomy is the method of treatment offering the best chance for improvement to the hypertensive patient today, still it would be unwise to leave the reader with the impression that this operation is free from risk or postoperative complications. Intercostal neuralgia with considerable discomfort for several months not uncommonly develops. Postural hypotension and at times actual syncope in the upright position as a result of vasodilatation in the splanchnic bed may prove troublesome, but can frequently be counteracted by a snugly fitting supportive abdominal corset. Complications involving the pleural cavity are among the more serious immediate postoperative disturbances, and the clinician must constantly be on the alert for sterile effusions, empyema, and tension pneumothorax. In general, the greater the skill and experience of the surgeon performing the operation, the less often will these pleural complications be encountered.

While the surgeon continues in his efforts toward improving his operative technic and working out the most effective type of resection, upon the internist must fall the task of attempting to select hypertensive patients most suitable for operative treatment. There are no absolute criteria as to which patients are good candidates for the operation. In order to aid in the selection of patients most likely to benefit from the operation and to facilitate the study of such patients, as well as to make controlled observations by which the success of the operation may be measured, Thomas and her associates [5] have outlined a program designed to standardize the preoperative investigations. In the preliminary selection of patients for operation, this group considers that young individuals with hypertension (blood pressure over 150 mm. Hg systolic and 90 mm. diastolic) who have either

[4] Rojas, F., Smithwick, R. H., and White, P. D.: Nonspecific major operations and lumbodorsal sympathectomy: a comparison between their effects upon the blood pressure, Jr. Am. Med. Assoc., 1944, cxxvi, 15–17.

[5] Thomas, C. R., and associates: Personal communication.

begun to get into difficulties from their hypertension or have asymptomatic hypertension of extreme degree must be seriously regarded as potential candidates. They list the principal contraindications as follows: asymptomatic hypertension unless the blood pressure is extremely high, marked renal insufficiency, age over 50 years, chronic renal disease, coarctation of the aorta, and advanced arterial diseases. Although these are some of the more common reasons to advise against operation, they are not necessarily absolute; other contraindications will be found in individual cases. Among the preliminary studies which may be carried out while the patient is ambulatory, Thomas lists: serologic test for syphilis, blood count, urine examination, blood non-protein nitrogen, sugar, and cholesterol, phenolsulfonphthalein test, electrocardiogram, teleoroentgenogram of heart, and intravenous pyelogram. After these studies have been completed, certain patients can be eliminated at once as candidates for sympathectomy. Those who still appear eligible should be admitted to the hospital as bed-patients for further investigation, provided the patient has signified his willingness to undergo surgery should he prove suitable. It is recommended that the following studies be carried out while the patient is hospitalized: urea clearance, urine concentration test, urine culture, photographs of optic fundi, chart of daily resting blood pressure, cold pressor test, sedation test, postural blood pressure response, vital capacity, venous pressure, circulation time, and cardiac output. Once this mass of clinical data has been assembled, the physician and surgeon together have a wealth of objective information on which to base their final decision as to the advisability of operation. It is important that candidates be worked up and operated upon as promptly as possible since certain patients may suffer from cerebral accidents while waiting for the studies to be completed.

Perhaps the invasion of the surgeon into the therapy of hypertension—staple of pure "medical" diseases since time immemorial—may come as a disturbing jolt to many an internist and cardiologist. But we internists must frankly confess that we have been able to accomplish relatively little in the alleviation of hypertension beyond teaching the unfortunate victim how to live with his disorder rather than to fret himself into a premature stroke. Therefore, let us graciously stand back and say, More power to the surgeon! For, after all, the transfer of the therapy of hypertension to the surgeon may rightly be regarded as divine retribution for the manner in which the internist with his sulfonamides and penicillin has wafted many a potential victim away from the surgeon's knife.

W. H. B.

REVIEWS

Physical Foundations of Radiology. By Otto Glasser, Ph.D., Edith H. Quimby, Sc.D., Lauriston S. Taylor, Ph.D., and J. L. Weatherwax, M.A. 426 pages; 19 × 13.5 cm. 1944. Paul B. Hoeber, Inc., New York. Price, $5.00.

Although it covers the field of physical radiology rather completely, it would be difficult to recommend this volume to roentgenologists. The several authors who have written this book must have done so for those who have had considerable training in radiation physics. Those who are not fortunate enough to have had such training will find this book incomplete in its explanations, and rather confusing. The writers plunge directly into physics (which at best is dull reading), neglecting to elucidate the more fundamental aspects of radiology. To one seeking knowledge of radiology, this lack of explanations causes the book to be very rugged reading.

Each author contributes several chapters to the volume, discussing many things, such as measuring roentgen units, the various ways of doing so, the biological effect of irradiation, tissue dose calculation, filtration of both roentgen-rays and radium. The cyclotron is mentioned and a brief discussion is added concerning the radioactivity of elements following bombardment by this machine. Radium and its various decomposition products are described, as well as filtration and tissue dosage of this element. As will be noted from this brief list of subjects covered, many important matters are discussed. This would indeed be an excellent volume if the writers did not assume that the reader is quite conversant about radiation physics. It is not recommended.

D. J. B.

Fundamentals of Pharmacology. For Students and Practitioners. By Clinton H. Thienes, M.D., Ph.D., Professor of Pharmacology, University of Southern California. 497 pages; 15 × 22 cm. 1945. Paul B. Hoeber, Inc., New York 16, N. Y. Price, $5.75.

This text designed for students of medicine and physicians is an up-to-date volume. The aim of the author has been to reduce the large volume of pharmacologic literature to fundamentals and to present the material in concise terms. In the words of Dr. Thienes the choice of material has been governed by the fact that pharmacology is taught before the medical student has had clinical experience, therefore, a complete discussion of therapeutic uses of drugs has not been attempted. The arrangement of the text is novel. Stimulants of the central nervous system are first considered and then the central nervous system depressants. In section three, drugs acting on the peripheral nervous system are discussed followed by drugs acting on muscles, antiparasitic drugs, hormones, vitamins, locally acting substances, diagnostic agents, the action of drugs on cells and finally prescription writing. Following this plan one finds a discussion of digitalis under drugs acting on muscles; sulfonamides and antibiotics are considered in the section dealing with antiparasitic drugs; epinephrine, however, is considered in the section with sympathomimetic drugs and not with the hormones. With this condensed form the author has managed to preserve a readable style and even such subjects as cellular structure and metabolism in relation to pharmacology have received rather detailed consideration. The author is to be congratulated upon the text as a whole and teachers may recommend this book to students without reservation.

J. C. K., Jr.

BOOKS RECEIVED

Books received during May are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Fundamentals of Pharmacology. By CLINTON H. THIENES, M.D., Ph.D., Professor of Pharmacology, University of Southern California School of Medicine. 497 pages; 15 × 22 cm. 1945. Paul B. Hoeber, Inc., New York. Price, $5.75.

Transactions of the Association of American Physicians. Fifty-Eighth Session, held at Atlantic City, N. J., May 9, 1944. Volume LVIII. 1944. Published for the Association, Philadelphia. 204 pages; 15.5 × 23 cm.

The Fundamentals of Electrocardiographic Interpretation. Second Edition. By J. BAILEY CARTER, M.D., F.A.C.P. 406 pages; 14.5 by 21.5 cm. 1945. Charles C. Thomas, Baltimore and Springfield. Price, $6.00.

Constitutional Medicine and Endocrinology. Edited by E. PULAY, M.D., A. P. CAWADIAS, O.B.E., M.D., F.R.C.P., and P. LANSEL, M.D. Volume I. 99 pages; 16 × 25 cm. 1944. 10s. 6d. net.

Biological Symposia. Vol. XI. Ageing and Degenerative Diseases. Edited by ROBERT A. MOORE. 242 pages; 17.5 × 25 cm. 1945. The Jaques Cattell Press, Lancaster, Pa. Price, $3.00.

Universidad de Antioquia. Numero 69. 1945. Medellin-Colombia.

Myasthenia Gravis. By ADALBERTO R. GOÑI. 1944. "El Ateneo." Buenos Aires.

COLLEGE NEWS NOTES

New Life Members

Since the publication of the last issue of the Annals of Internal Medicine, the following Fellows of the College have become Life Members:

Dr. Vernon L. Evans, Aurora, Ill.
Dr. Harry J. Friedman, Seattle, Wash.
Dr. Mark Alexander Griffin, Asheville, N. C.
Dr. William Ray Griffin, Asheville, N. C.
Dr. Sydney E. Johnson, Louisville, Ky.
Dr. Frank B. Marsh, Salisbury, N. C.
Dr. Fred M. F. Meixner, Peoria, Ill.

A. C. P. Members in the Armed Forces

Dr. Lawrence N. Durgin, F.A.C.P., Amherst, Mass., is a Major in the U. S. Army, having been on duty since July 15, 1941, but not previously recorded with the College. Reported in the June News Notes section of this journal was a total of 1,858 Fellows and Associates of the College on active military duty. In addition to Dr. Durgin, the following members have since reported for active duty, bringing the total to 1,863.

Joseph David Croft
Robert A. Edwards
Clayton B. Ethridge
M. Hill Metz

The following members of the College have been honorably discharged:

Michael A. Cogan, Captain, (MC), AUS—Springfield, Mass.
John B. D'Albora, Lieutenant Colonel, (MC), AUS—Brooklyn, N. Y.
A. N. Fregeau, Lieutenant Commander, (MC), USNR—San Francisco, Calif.
Lee Pettit Gay, Major, (MC), AUS—Lincoln, Nebr.
Robert Collier Page, Lieutenant Colonel, (MC), AUS—New York, N. Y.

Gifts to the College Library

The following gifts of publications by members are gratefully acknowledged:

Irving L. Applebaum, F.A.C.P., Lieutenant Colonel, (MC), AUS—4 reprints
Dr. Benjamin M. Bernstein, F.A.C.P., Brooklyn, N. Y.—1 reprint.
Dr. Harry R. Litchfield, F.A.C.P., Brooklyn, N. Y.—1 reprint.
Dr. Thomas Hodge McGavack, F.A.C.P., New York, N. Y.—4 reprints
Dr. Lawrence E. Putnam (Associate), Washington, D. C.—1 reprint.
Dr. Robert M. Stecher, F.A.C.P., Cleveland, Ohio—6 reprints.

Dr. John M. Swan, F.A.C.P., Rochester, N. Y., on behalf of the New York State Committee of the American Society for the Control of Cancer, has donated to the College Library, Volumes 1 and 2 of "The Pith of Recent Cancer Literature."

Autumn 1945 Schedule, Postgraduate Courses

The Advisory Committee on Postgraduate Courses, with the approval of the Board of Regents, June 10, 1945, announces the following schedule of courses sponsored by the American College of Physicians during the autumn of 1945:

Allergy—Roosevelt Hospital, New York City, Dr. Robert A. Cooke, Director; one week: Oct. 8–13.

Internal Medicine—University of Michigan Medical School, Ann Arbor, Dr. Cyrus C. Sturgis, Director; two weeks: Oct. 22–Nov. 3.

General Medicine—University of Oregon Medical School, Portland, Dr. Homer P. Rush, Director; one week: Oct. 29–Nov. 3.

Recent Advances in the Diagnosis and Treatment of Cardiovascular Disease—Massachusetts General Hospital, Boston, Dr. Paul D. White, Director; one week: Nov. 5–10.

Advanced Cardiology—Philadelphia General Hospital, Philadelphia, Dr. Thomas M. McMillan, Director; one week: Nov. 26–Dec. 1.

Endocrinology—University of Illinois College of Medicine, Chicago, Dr. Willard O. Thompson, Director; one week: Nov. 5–10.

Gastro-Enterology—University of Chicago, Dr. Walter L. Palmer, Director; one week: Nov. 12–17.

The course "Recent Advances in the Diagnosis and Treatment of Cardiovascular Disease" will be largely a repetition of a similar course given by Dr. White during the autumn of 1944, when the course was greatly oversubscribed. Registrants who could not be accepted in 1944 for this course will be given first choice in 1945. A great host of registrations have already been received, owing to previous announcements in this journal, and it is already definitely established that the College will be unable to accommodate any non-members in this course—in fact, unless the Office of Defense Transportation removes present restrictions of fifty out-of-town registrants, the course must be considered filled to capacity.

The course in "Internal Medicine" at Ann Arbor will cover various phases of internal medicine and will be presented largely as an advanced course. The course will be valuable for returning physicians from the armed forces as a review course; for physicians preparing for American Board examinations; and practicing physicians desiring a refresher course. It will not be possible to register physicians except for the full course; that is, no registrations will be accepted for one week, for by so doing other physicians would be kept out.

The course in "General Medicine" at the University of Oregon Medical School will be primarily a repetition of the very fine course given at that institution for the College in 1944. A competent faculty and an excellent program have been organized. The selection of papers and subjects will be timely and interesting. Several special features will be arranged. Those taking the course previously were high in their praise. This course should be well supported by the College membership in the far western part of the United States and Canada.

The course in "Allergy" given by Dr. Robert A. Cooke will be largely a repetition of the excellent courses Dr. Cooke has given repeatedly for the College during recent years. Nowhere in the country is such a valuable course available, condensed into a short period.

For the first time the College has organized and scheduled a course in "Advanced Cardiology," which will be open only to registrants with an adequate back-

ground in general cardiology. It will be presupposed that all registrants will be interested in the advanced phases of this specialty. The Director, Dr. McMillan, will supplement the local Philadelphia faculty with some outstanding authorities in the field from other cities and the registration will be held to a comparatively small group.

The course in "Endocrinology" by Dr. Willard O. Thompson is a repetition of other fine courses Dr. Thompson has organized and given for the College. His experience and enthusiasm are guarantees of the finest course procurable in this specialty.

The course in Gastro-enterology is organized to fill the steady demand for courses in this field. The Director, Dr. Palmer, will organize a course along sound and reliable principles, and a maximum registration is anticipated.

The Postgraduate Bulletin with registration forms will be mailed to all members of the College in the late summer or early autumn. Where facilities are available, courses will be open also to non-members of the College who have adequate preliminary training; preference to be given to non-members in the following order: (1) Candidates for membership; (2) Medical officers in the armed forces; (3) Physicians preparing for examinations by certifying boards; (4) Other non-members having adequate background for advanced work.

Especially is it the desire of the College to serve as many as possible of physicians retiring from active service in the armed forces. The Postgraduate Courses of the College are part of its war and postwar plans. The tuition fee for all courses will be: For members—$20.00 per week; For non-members—$40.00 per week; For medical officers of the armed forces of the United States and Canada—Free.

Report from the Office of the Surgeon General, U. S. Army

Personnel Release Policy

Substantial releases of Army Medical Department personnel will not take place before the latter part of this year, Surgeon General Norman T. Kirk said in announcing a policy on discharges in conformity with War Department procedures. This is due to the fact that the peak of the Medical Department's activities will not be reached until fall.

In formulating the policy, consideration was given to civilian needs for professional medical, dental and veterinary care without weakening military needs. Other factors considered were the length of time necessary for personnel to complete their work in the Mediterranean and European Theaters and return to the United States; replacement of Medical Department personnel in active theaters by those who have not had overseas duty; necessity for the maintenance of a high standard of medical care; the heavy load of patients in the United States; evacuation of the sick and wounded from Europe in the next 90 days and continuing medical service in the Pacific.

The policy applies with equal effect to Army medical officers assigned to the Veteran's Administration and other agencies.

Medical Corps

a. Officers whose services are essential to military necessity will not be separated from the service.

b. Officers above 50 years of age whose specialist qualifications are not needed within the Army will receive a high preferential priority for release from active duty.

c. Adjusted Service Ratings will be utilized as a definite guide to determining those who are to be separated.

Acting Secretary of War Patterson and General Kirk Report on Health of Army

Honorable Robert P. Patterson, Acting Secretary of War, in presenting Major General Norman T. Kirk, F.A.C.P., Surgeon General of the Army, at a radio and press conference on May 24, made the following points:

Despite the problems of fighting in virtually all parts of the world and in caring for the largest American Army in history, no army at any time in history has achieved a record of recovery from wounds and freedom from disease comparable to that of the American Army in this war; 97 out of every 100 men wounded in battle who reach a hospital have been saved; 70 out of every 100 men wounded overseas were returned to duty and 27 were evacuated to this country; during the past three years less than one death per 1,000 men per year has resulted from disease; malaria has been reduced from hundreds of cases per 1,000 men per year to less than 50; the dysenteries have occurred among less than 90 among every 1,000 men per year and have been readily controlled; physical examinations are being given to each of the 3,500,000 soldiers in the European and Mediterranean theaters before they are redeployed; Medical Department personnel will be sent to the Pacific in ever-increasing numbers; the peak of the Medical Department's activities will not be reached until autumn, 1945; wounded and sick are being returned to this country from all theaters at the rate of 44,000 per month; 7 additional hospital ships, bringing the total to 29, with an aggregate patient capacity of 20,000, have been provided for the evacuation of patients from Europe to this country; special hospital equipment has been placed aboard 24 troop transports, giving the Army an additional patient-carrying capacity of 40,000; 8,000 patients a month are being brought back to the United States by plane; the population of all Army hospitals in the United States at present is 290,000, which is expected to reach 315,000 by September.

Mr. Patterson said in part:

"No greater tribute can be paid to the Medical Department of our Army than the tribute paid by its record of saving lives in this war."

General Kirk reported in part as follows:

"The Army Medical Department is well prepared to maintain its record of saving lives and guarding against disease in the second phase of World War II which will be centered in the Pacific. As combat activities increase in that area troops moved from European theaters will find a different type of warfare, different diseases and different methods of combating disease.

"The Medical Department has been preparing for years for its fight on disease in the Pacific. In addition to its intensive research into diseases common to that area it has gained much value in practical application of its methods from the campaigns already fought.

"In the Pacific areas our fighting men are exposed to many types of disease that are rare in the United States and Europe. However, this should not be considered cause for alarm. With proper preventive measures and medical service the disease rate in the Pacific will be kept to a minimum.

"Every fighting unit in the Pacific area has had the same type of medical organization accompanying it as those in other theaters. The chain of evacuation of the wounded is well organized and is very effective. Because of geographical and climatic differences certain changes were desirable, but the same high type facilities are available.

"The main diseases to be encountered in the Pacific are malaria, the dysenteries, scrub typhus, skin infections, schistosomiasis, filariasis and dengue fever. Excellent progress has already been made in keeping the incidence of all of these diseases to a very low degree.

"Malaria, for example, has been reduced to one-fourth its incidence in the early part of the war so that the overall death rate from malaria in the Army is .01 per cent.

"The use of D.D.T. and atabrine is primarily responsible for lowering the incidence rate of the most disabling tropical diseases. The remarkable record in lowering the malaria rate is due also to strict discipline and control measures. Malaria is spread by the anopheles mosquito. D.D.T., a recently developed insecticide, is used to kill this mosquito and the larva. Areas are sprayed with D.D.T. by plane and a five per cent solution of D.D.T. sprayed on barracks walls in kitchens and huts kills all mosquitoes and flies alighting thereon for months after spraying.

"The dysenteries, so common in the Pacific areas, which are spread by flies are also rendered less prevalent by the use of D.D.T.

"Atabrine has been found more effective as a therapeutic agent in the control of malaria than quinine.

"Filariasis, which is also spread by the mosquito, is reduced by the use of D.D.T. and mosquito control methods.

"Schistosomiasis is caused by a small fluke found in pools and running streams which in a matter of seconds burrows through the skin and infects the individual. All water found to contain these flukes is posted and personnel is warned not to bathe, wade or wash in it.

"Areas found to contain scrub typhus are immediately burned over, clothing is impregnated, and efforts are being made to develop a vaccine to counteract it.

"Dengue fever, also spread by the mosquito, is controlled by the use of D.D.T. and mosquito abatement.

"It can readily be noted that D.D.T. is one of the miracle developments of this war.

"Last year a tropical disease center was opened by the Army Medical Department at Moore General Hospital, Swannanoa, North Carolina. It was designated as a center for the study and treatment of tropical diseases. This center has assisted greatly in the investigation and treatment of these diseases and has reduced the loss of manpower as a result of illness, thereby making an important contribution to the continuing improvement of American medicine.

"In addition to protecting the soldier from diseases of the tropics the Army Medical Department is affording all possible protection against disease and harmful pests which might be brought into the United States by military traffic. This is done through a quarantine branch which works in conjunction with the U. S. Public Health Service and the Navy.

"The Army program includes measures to prevent the importation of dangerous insects from abroad. Extensive insect control programs have been carried out about military stations and airports abroad, using highly effective techniques and agents. Passengers, planes, ships and cargo are sprayed with insecticides in order to eliminate insect risk.

"The battle is also waged through the control of rats and vermin. The most effective means of ridding ships of rats has been to build ships in such a way that rats cannot live or breed aboard them. Modern American ships are practically free of this age-old problem.

"To protect the country against agricultural diseases and pests which might be imported, rigid restrictions and inspections are made fully effective for military traffic. Particular stress is laid upon packing materials which might harbor insect forms.

"The Army Medical Department has complete medical and sanitary surveys of all the territory in the Pacific which is potential battle ground. The health hazards to soldiers are known to the Medical Corps officers who accompany all invasion troops and that knowledge is distributed to all the men.

"The Army Medical Department has been doing a fine job in the Pacific and will continue to do that job as activities in that theater increase. It is true that the

pestilential islands of the Pacific have not been changed into gardens of Eden, but when the deplorable health conditions that existed there are compared with what has been accomplished it is obvious that our victory over the Japs will be hastened.

"While all of this work and planning was going on for the increased activity in the Pacific the Army Medical Department during 1944 took care of 4,435,000 patients in hospitals—2,315,000 in the United States and 2,120,000 in hospitals overseas. In addition it provided care for an additional 43,210,000 non-hospitalized patients—those with minor infections and injuries who were only temporarily incapacitated.

"It performed the essential functions of caring for men wounded in battle, the injured and the sick to maintain fighting strength with 45,000 medical corps, 15,000 dentists, 52,000 nurses, 2,000 veterinarians, 18,700 medical administrative corps men, 2,500 sanitary corps specialists, 1,000 physical therapists, 1,500 dietitians, 61 pharmacy corps officers, 535,000 enlisted medical aid men and approximately 80,000 civilian employees.

"Illness and recuperation of wounded and injured men does not cease with a formal declaration of the end of hostilities on any front. The care of these men and women is a continuing responsibility of the Medical Department which will go on for many months in the future. It will increase rather than diminish during the remainder of 1945, according to the best estimates which can be made now. Therefore, as I have said before, medical care by the Army has yet to hit its full stride. One thing I wish to promise is that the best scientific medical attention will continue to be furnished to every man needing it."

Colonel Eppinger Returns to U. S.

Colonel Eugene Eppinger (Associate), (MC), AUS, formerly of Brookline, Mass., recently returned to this country from the Philippines where he was Assistant Consultant in Medicine in the Southwest Pacific Area of Operations.

Colonel Youmans and Dr. Wearn Survey Pacific Area Nutrition Problems

Colonel John B. Youmans, F.A.C.P., Director of the Nutrition Division, Preventive Medicine Service, Office of The Surgeon General, and Dr. Joseph T. Wearn, F.A.C.P., of Cleveland, Civilian Consultant to The Surgeon General, returned in May from an extended nutritional survey of the islands in the Pacific Ocean area during which they consulted with General MacArthur. They instituted a study on the nutrition of troops in the area and on diseases which may have a nutritional origin.

Recent Promotions, Medical Corps Officers

Lieutenant Colonel to Colonel:

John Sinclair Denholm (Associate), Burlington, N. C.

Major to Lieutenant Colonel:

Lee Herman Leger (Associate), Kansas City, Kan.
George Carson McEachern (Associate), Long Island, N. Y.
Arthur Dale Nichol, F.A.C.P., Shaker Heights, Ohio
Oscar Armand Palatucci (Associate), New York, N. Y.

Philippine Bureau of Science Totally Destroyed

The Philippine Bureau of Science, Manila, which was the principal center of research work in the Philippines, is reported to have been totally destroyed by the Japanese. This bureau housed the most important scientific library in the islands and was the publication headquarters of the Philippine Journal of Science. It contained thousands of specimens of Philippine and other Asiatic plants, birds, mammals, insects, etc. The School of Medicine, the School of Hygiene and Public Health and the entire plant of the University of the Philippines, the Philippine General Hospital, the Weather Bureau and the Philippine National Library were located in the same general area, and these buildings, for the most part, and everything of scientific value, have been destroyed or very badly damaged.

Penicillin Tablets for Civilian Use Now Available in Mexico

For the first time penicillin in tablets for commercial purposes has gone on sale. U. S. producers of penicillin must await lifting of the W.P.B. restrictions before they can begin producing the drug in pills and ointments for commercial purposes. However, the Mexican government has granted permission to its sole commercial producer, Wyeth-Stille, S.A., of Mexico City, affiliate of Wyeth Incorporated of Philadelphia, to manufacture penicillin in tablets and make them available for civilian use immediately. The tablet is packed in vials containing five tablets of 20,000 units each. The vials contain a desiccant which absorbs moisture, allowing the penicillin to remain stable for six months or more, it is claimed. Just as soon as W.P.B. gives permission, penicillin for oral administration will be placed on the market in the United States.

Elections to A. C. P. Membership by Board of Regents, Philadelphia, June 10, 1945

Elections to Fellowship

Annis, Jere Wright, Lakeland, Fla., AUS

Banks, Roland Wellington, Philadelphia, Pa., AUS
Bardon, Richard, Duluth, Minn.
Beckwith, Julian Ruffin, Charlottesville, Va., AUS
Benson, Otis Otto, Jr., U. S. Army
Bondurant, Charles Palmer, Oklahoma City, Okla.
Bradford, Aubrey LeVerne, U. S. Army
Broun, Coronwy Owen, St. Louis, Mo.

Campbell, Donald Clarence, Rochester, Minn., AUS
Chamberlain, Eugene Charles, Fort Lauderdale, Fla.
Chamberlin, Donald Tillinghast, Boston, Mass., AUS
Coffelt, Ralph L., Waco, Tex., USNR
Crandall, Lathan Augustus, Jr., Germantown, Tenn.

Dearing, William Hill, Rochester, Minn.
Detweiler, Herbert Knutsen, Toronto, Ont., Can.
Dock, William, New York, N. Y.
Dolger, Henry, New York, N. Y.

Dreessen, Waldemar Claus, U. S. Public Health Service
Durham, J(ames) Richard, Jr., Wilmington, Del., AUS

Elliott, F(rederick) George, Edmonton, Alta., Can., RCAMC

Fenn, George Karl, Chicago, Ill.
Ferguson, John Howard, Chapel Hill, N. C.
Ferris, Eugene Beverly, Jr., Cincinnati, Ohio.

Garrison, George Harry, Oklahoma City, Okla.
Ginsberg, Harold Isadore, Detroit, Mich., AUS
Graham, William Donald, U. S. Army
Graves, Herman Coddington, Grand Junction, Colo.
Gubner, Richard Sigmund, Brooklyn, N. Y.

Hamilton, Charles Edward, Lafayette, La.
Hemphill, Roger Andrew, Mt. Morris, N. Y.
Hill, Joseph MacGlashan, Dallas, Tex.
Hobbs, Robert Emmett, Shenandoah, Pa., AUS
Hoxie, Harold Jennings, Los Angeles, Calif.

Kalkstein, Mennasch, New York, N. Y., AUS
Karr, J(ohn) Kenneth, Milwaukee, Wis.
Kauvar, Solomon Salkind, Denver, Colo.
Keane, Roger Hunter, Portland, Ore., USNR
Keliher, Thomas Francis, Washington, D. C.
Kendell, H(erbert) Worley, Chicago, Ill., USPHS (R)
Kiene, Hugh Edward, Providence, R. I., AUS
Kinsell, Laurance Wilkie, East Stroudsburg, Pa., USNR
Kinsey, Harold Ivan, Toronto, Ont., Can.
Kirshbaum, Jack D., Chicago, Ill., AUS
Krell, Solomon, New York, N. Y.

Leinoff, Harry D., New York, N. Y., AUS
Leonard, John Charles, Hartford, Conn.
Lidman, Bernard Isaac, Norfolk, Va., AUS

Mackay, Roland Parks, Chicago, Ill.
Marion, Donald Feige, Detroit, Mich., AUS
Matthews, Robert Archibald, Philadelphia, Pa.
Matzner, Milton John, Brooklyn, N. Y., USNR
Mays, John Richard Shannon, Milledgeville, Ga., AUS
McCombs, Robert Pratt, Jenkintown, Pa., USNR
McHardy, George Gordon, New Orleans, La.
McManus, John Francis, Boston, Mass., AUS
McReynolds, Ralph, Quincy, Ill.
Meyer, Paul Reims, Port Arthur, Tex.
Miller, David Kimball, Buffalo, N. Y.
Miller, Raymond Everett, New York, N. Y., USNR
Millman, Max, Springfield, Mass.
Mitchell, William John, Los Angeles, Calif., AUS
Moore, George Barnard, Jr., U. S. Army
Murphy, Martin Alvin, Brooklyn, N. Y.
Murphy, Willis Aloysius, New York, N. Y., USNR

Noth, Paul Henry, Grosse Pointe Farms, Mich.

Orgain, Edward Stewart, Durham, N. C.

Parsons, Ernest Holden, U. S. Army
Paulus, David Dare, Oklahoma City, Okla.
Perlman, Frank, Portland, Ore., AUS

Query, Richard Zimri, Jr., Charlotte, N. C., AUS

Rascoff, Henry, Brooklyn, N. Y.
Rash, Jack Otway Watkins, Miami, Fla., AUS
Richards, Dickinson Woodruff, Jr., New York, N. Y.
Robinson, Albert Henry, U. S. Army
Robinson, William Dodd, Ann Arbor, Mich.
Ross, Harry Plummer, Richmond, Ind.
Ryan, Joseph Maurice, St. Paul, Minn., AUS

Schweiger, Lamont R., Milwaukee, Wis., AUS
Serra, Lawrence Mario, Baltimore, Md.
Shaw, James Raymond, U. S. Public Health Service
Sherman, E(dward) David, Sydney, N. S., Can.
Silvers, Seymour Harry, Brooklyn, N. Y.
Slutzky, Ben, Omaha, Nebr.
Smith, David Tillerson, Durham, N. C.
Smith, Lucian Anderson, Rochester, Minn., AUS
Spessard, Thomas Nathaniel, Norfolk, Va., USNR
Sprunt, Douglas Hamilton, Memphis, Tenn.
Stringer, Christopher James, Lansing, Mich.

Thomas, George Carroll, U. S. Navy
Tiber, Arthur Martin, New York, N. Y., AUS
Tillman, Richard Nelson, Baltimore, Md.
Twiss, Arthur Raymond, Oakland, Calif., AUS

Valdez, Frank Carl, Chicago, Ill.
Vander Veer, Joseph Bedford, Philadelphia, Pa., AUS
Vass, Aloysius, Springfield, Ill., AUS

Warren, Leon Hugh, Washington, D. C., AUS
Williams, Alton Floyd, Metter, Ga., AUS
Wintrobe, Maxwell Myer, Salt Lake City, Utah
Wood, W(illiam) Barry, Jr., St. Louis, Mo.
Woody, McIver, New York, N. Y.
Wright, Scheffel Hays, Miami, Fla.

Elections to Associateship

Alpher, Isadore Meyer, Washington, D. C.

Baker, Elsworth Fredrick, Marlboro, N. J.
Barker, Charles Scott, Montreal, Que., Can.
Barker, Joseph Michael, Washington, D. C.

Baube, John Louis, Mt. Vernon, Ohio, AUS
Bayles, Theodore Bevier, Boston, Mass., AUS
Beebe, John Taylor, Hartford, Conn.
Bender, Morris Boris, New York, N. Y., USNR
Bennett, Raymond Edward, St. John's, Newfoundland
Berry, Maxwell Glen, Kansas City, Mo., AUS
Bishop, Ernest Wade, Providence, R. I.
Bosse, Milton Dietrick, Pittsburgh, Pa.
Brethauer, Edward Albert, Jr., Pittsburgh, Pa.
Brown, Morton Goodwin, Boston, Mass., AUS
Burdon, Phyllis Josephine, Seattle, Wash.
Butler, Fred Arthur, U. S. Navy

Cannon, Jesse Floyd, Salt Lake City, Utah
Cantor, Mortimer Jacob, Brooklyn, N. Y., AUS
Chinn, Austin Brockenbrough, Washington, D. C., AUS
Connor, Charles Ashley Richard, New York, N. Y., AUS
Crowe, William Roland, Jr., Atlanta, Ga.

Doak, Edmond King, Houston, Tex.
Donohue, William Michael, Houston, Tex., AUS
Durkee, Ralph Everett, Jr., Hartford, Conn., USPHS (R)

Edgar, Irving Iskowitz, Detroit, Mich.

Feinstein, Marcus Abraham, New York, N. Y., AUS
Finegan, Rexford William, New York, N. Y., AUS
Flaum, Gerald, New York, N. Y., USNR
Fleishman, Alfred, St. Louis, Mo., AUS
Fleiss, Arthur Nathan, Syracuse, N. Y.
Freireich, Abraham Walter, Malverne, N. Y.
Friedgood, Harry Bernard, Los Angeles, Calif.

Gold, Rubin Leonard, San Francisco, Calif., AUS
Goldner, Martin Gerhard, Chicago, Ill., AUS
Gordon, Marie Dannenbauer, San Antonio, Tex.
Greist, John Howard, Indianapolis, Ind., AUS
Gunther, Lewis, Los Angeles, Calif., USNR

Hammerstrom, Carl Frederick, Jamestown, N. Y., AUS
Hampton, Hiram Phillip, Tampa, Fla., AUS
Hanss, Armand William, Springfield, Mo., AUS
Havell, Robert Barron, Washington, D. C.
Hawirko, Leonora, Edmonton, Alta., Can.
Heineken, Theodore Stanley, Bloomfield, N. J., AUS
Hodas, Joseph Henry, New York, N. Y., USNR
Hoffman, Samuel J., Chicago, Ill., AUS
Horner, John Linscott, St. Louis, Mo.
Hull, Wayne McKinley, Omaha, Nebr.
Hyman, Samuel, Utica, N. Y.

Johnson, Artell Egbert, New York, N. Y.
Johnson, Ralph Arthur, Detroit, Mich.

Katz, Sol, Washington, D. C.
Knudson, Alvin Bernt Clifford, Dwight, Ill., AUS
Kohlstaedt, Kenneth George, Indianapolis, Ind.
Korth, Zeno Nicholas, Omaha, Nebr., AUS
Kreitz, Paul Brooks, Bethlehem, Pa.
Krygier, John Joseph, Portland, Ore.
Kugel, Victor Harris, New York, N. Y., AUS

Lamb, John Henderson, Oklahoma City, Okla.
Laufer, Srul Tul, Halifax, N. S., Can.
Leary, William Vincent, Rochester, Minn., AUS
Lease, Raymond Essex, Oyster Bay, N. Y.
Leech, Elfred Llewellyn, Oneonta, N. Y.
Lenton, Herbert P., Carlisle, Pa., AUS
Levin, William Cohn, Galveston, Tex.
Lindauer, Max August, Philadelphia, Pa., AUS
Lubitz, Joseph M., Chicago, Ill. USPHS (R)
Lueck, Arthur George, U. S. Navy

Macdonald, James William, Detroit, Mich.
Marra, John James, Albany, N. Y.
Mauser, Carl Louis, Berkley, Calif.
McKinley, Wesley Frank, Jr., Galveston, Tex.
McLemore, Harold Hiques, Spokane, Wash., AUS
Mendlowitz, Milton, New York, N. Y., AUS
Miller, Sidney, Rochester, Minn., AUS
Moss, John Edward, U. S. Navy
Murphy, Franklin David, Philadelphia, Pa., AUS

Palatucci, Oscar Armand, New York, N. Y., AUS
Paris, Marcus, South Norwalk, Conn.
Paul, Jerome Thomas, Chicago, Ill., AUS
Payne, Russell Crandle, Washington, D. C.
Prigal, Samuel Jeremiah, New York, N. Y.

Rawling, Frank Frederick Archibald, Ann Arbor, Mich.
Resch, Joseph Anthony, U. S. Army
Rice, Raymond Lester, Milwaukee, Wis.
Robertson, Elmer Shackleford, Richmond, Va., AUS
Rodriguez-Olleros, Angel, San Juan, P. R.
Rogers, Hobart, Oakland, Calif.
Ryan, Edward Joseph, Cleveland, Ohio, USNR

Salmon, George Wilbur, Houston, Tex.
Sanders, Alexander, Chicago, Ill., AUS
Schaefer, Bertram Francis, Washington, D. C.
Schwartz, Robert, Aspinwall, Pa., AUS
Shullenberger, Wendell Arthur, Indianapolis, Ind.
Silverman, Jacob Joseph, Staten Island, N. Y., AUS
Simpson, Roger Graham, San Francisco, Calif., AUS
Sklaver, Joseph, Waterbury, Conn., AUS
Sokolow, Maurice, San Francisco, Calif., USNR
Straumfjord, Jon Vidalin, Astoria, Ore.

Vidgoff, Ben, Portland, Ore.
Vyner, Harold Lawrence, Brentwood, N. Y., AUS

Walker, Edmund Frank, Worcester, Mass., AUS
Weedon, Frederick Renfroe, Jamestown, N. Y.
Weig, Clayton George, Buffalo, N. Y.
Westra, Jacob John, Champaign, Ill.
Wexler, Jack, Boston, Mass., AUS
Wheeler, William Louis, Jr., New York, N. Y.
Wilson, Sloan Jacob, Columbus, Ohio, AUS
Wright, Jackson White, Cincinnati, Ohio, AUS

Lieutenant Colonel Kendall Elsom, F.A.C.P., is now Chief of the Medical Service at the Regional Hospital of the Army Service Forces at Fort Benning, Ga.

Lieutenant Colonel Charles M. Caravati, F.A.C.P., Chief of the Medical Service at the Woodrow Wilson General Hospital, Staunton, Va., addressed the Luzerne County Medical Society, May 16, on "The Regional non-Malignant Ulcerative Lesions of the Bowel."

Dr. Bernard L. Wyatt, F.A.C.P., for many years located at Tucson, Arizona, opened offices in the Fidelity Building, Los Angeles, California, on June 1.

On March 2, 1945, Dr. Howard Wakefield, F.A.C.P., and Dr. Selim W. McArthur, Chicago, presented a paper, "Further Observations on the Electrocardiogram during Experimental Distention of the Human Gall Bladder," before the Chicago Surgical Society.

On May 10, 1945, Dr. Herbert T. Kelly, F.A.C.P., Chairman of the Committee on Nutrition of the Medical Society of the State of Pennsylvania, presented before the Centre County Medical Society at Nittany Lion, State College, Pa., a paper on "Convalescent Care and Postoperative Management."

Dr. Theodore Rothman (Associate), formerly of Paterson, N. J., during May removed to Los Angeles where he opened his office for the practice of medicine at 2007 Wilshire Boulevard.

Medico-Legal Conference and Seminar
October 1–6, 1945, at Boston

The Department of Legal Medicine of the medical schools of Harvard, Tufts, and Boston University in association with the Massachusetts Medico-Legal Society will present a six-day program of lectures, conferences, and demonstrations having to do with the investigation of deaths in the interests of public safety. Attendance during five of the six days of the course will be limited to fifteen persons who have registered in advance. On one day (October 3) the program will be open to any physician, lawyer, police official, or senior medical student who may care to attend.

Further information may be obtained from the Secretary of the Massachusetts Medico-Legal Society, 25 Shattuck Street, Boston.

Lieutenant Colonel Leo V. Schneider, F.A.C.P., Associate Clinical Professor of Medicine at Georgetown University School of Medicine, Washington, and Chief Medical Officer at Glenn Dale Sanatorium, Glenn Dale, Md., was recently made Chief of Industrial Medicine at the New York Port of Embarkation.

Captain Lloyd R. Newhouser, F.A.C.P., delivered the 1945 Kober Foundation Lecture on "The Rôle of Whole Blood Plasma and Plasma Fractions in War Medicine" at Georgetown University School of Medicine, Washington, March 28. This marked the birthday of the late Dr. George M. Kober, F.A.C.P., who for many years was Dean of that institution and founder of this lecture. Captain Newhouser received an honorarium of $500. Vice Admiral Ross T. McIntire, Surgeon General of the Navy, presided.

Dr. Norman H. Jolliffe, F.A.C.P., has been made Chief of a new city-wide nutrition clinic at the lower East Side Health and Teaching Center of New York City.

Dr. Carl J. Wiggers, F.A.C.P., and his associates in the Department of Physiology, Western Reserve University, Cleveland, have received a grant of $8,200 from the Commonwealth Fund to continue studies on the peripheral circulation and shock during 1945–1946.

Captain Forrest M. Harrison, F.A.C.P., Chief of the Neuropsychiatric Division of the National Naval Medical Center, Bethesda, Md., has been given a special assignment to write the history of psychiatry in the Navy during World War II.

Captain Rolland R. Gasser Receives Bronze Star

Captain Rolland R. Gasser, F.A.C.P., formerly of Brooklyn, has been awarded the Bronze Star "for meritorious service to the United States as medical officer in command of a fleet hospital in the South Pacific area from March 31, 1944, to April 7, 1945. During this period Captain Gasser displayed exceptional ability in handling the many detailed medical problems which arose and worked tirelessly to establish and maintain excellent operating conditions throughout his command. By his initiative and thorough knowledge of medical administration he effected an efficient hospital service for the sick and wounded in the South Pacific and evacuees from adjacent areas. His leadership and professional skill were in keeping with the highest traditions of the United States Naval Service."

The Malcolm T. MacEachern Award

The Johnson and Johnson Research Foundation recently created an annual award at Northwestern University consisting of a silver medal and an honorarium of $250 to be known as the Malcolm T. MacEachern Award, in honor of Dr. MacEachern, a Fellow of the American College of Physicians, who is Associate Director of the American College of Surgeons and Director of the Program in Hospital Administration at Northwestern University. Johnson and Johnson has also announced a five-year grant of $75,000 to the program in hospital administration, including scholarships, to supplement $15,000 granted two years ago.

Dr. John F. Kenney, F.A.C.P., Pawtucket, R. I., has been installed as President of the New England Conference of Industrial Physicians.

Dr. Frederick A. Willius, F.A.C.P., Rochester, Minn., addressed the 76th Annual Session of the Canadian Medical Association at Montreal, June 11–15, his subject being "Critical Evaluation of Methods of Diagnosis in Cardiac Disease, with Special Reference to Electrocardiography."

Dr. Samuel J. McClendon, F.A.C.P., San Diego, was recently made President-Elect of the California Medical Association.

Dr. Harry L. Arnold, Jr. (Associate), of Honolulu, was one of the guest speakers at the meeting of the Association, his title being "The Diagnosis of Early Lepromatous and Neural Leprosy."

Dr. Leroy E. Burney (Associate), Regional Director of the U. S. Public Health Service, New Orleans, has been named State Health Commissioner and Secretary of the Indiana State Board of Health, his services having begun July 1, 1945.

Dr. Lewis J. Moorman, F.A.C.P., Oklahoma City, has been reëlected Secretary-Treasurer of the Oklahoma State Medical Association and will continue as Editor of its journal.

Dr. Howard T. Karsner, F.A.C.P., Professor of Pathology and Director of the Institute of Pathology, Western Reserve University, Cleveland, addressed the Los Angeles Academy of Medicine, May 11, on "Tumors of the Endocrine Glands."

Dr. Charles Walter Clarke, F.A.C.P., Executive Director of the American Social Hygiene Association, New York, has been reëlected Vice President of the National Health Council.

Dr. Russell H. Oppenheimer, F.A.C.P., as of June 1 resigned as Dean of Emory University School of Medicine, Atlanta. He had held the appointment for twenty years. Dr. Oppenheimer will continue his work as Professor of Clinical Medicine.

Dr. Eugene A. Stead, Jr., F.A.C.P., will serve as Acting Dean. Dr. Stead is also Professor of Medicine and Chairman of the Department.

Commander J. Roscoe Miller, F.A.C.P., Dean of Northwestern University Medical School, Chicago, is currently in charge of the Section on Internal Medicine, Professional Division of the Bureau of Medicine and Surgery, Washington, D. C. Upon his release from service, he will serve as Medical Director of the Chicago and Northwestern Railroad, in addition to his deanship at Northwestern University.

Dr. Joseph S. Evans, F.A.C.P., will retire as Professor of Medicine at the University of Wisconsin Medical School at the end of the current semester. He was the school's first professor of medicine. He is also Chairman of the Department of Medicine and has been with that institution since 1909.

Examinations in Pediatrics

The American Board of Pediatrics will conduct its fall written examination in various cities, under a monitor, October 19, 1945. The oral examination will be held in New York City, December 7–8, 1945.

Address the secretary, Dr. C. Anderson Aldrich, 115½ First Avenue, S.W., Rochester, Minn., for further details.

Captain Lyle J. Roberts, (MC), U.S.N., F.A.C.P., is reported still to be a prisoner of war of the Japanese, probably located in Manchukuo.

Commander William M. Silliphant, (MC), U.S.N. (Associate), was among medical officers rescued from Bilibid Prison Camp in Manila. He is now located at 129 N. Santa Anita Street, San Gabriel, Calif., but will soon be reassigned to new work in the Navy.

Dr. William C. Chaney, F.A.C.P., Memphis, was installed on April 8 as President of the Tennessee State Medical Association.

A Research Fellowship in Internal Medicine is being established at the University of Texas Medical Branch, Galveston, in honor of Dr. Marvin L. Graves, F.A.C.P., Emeritus Professor of Internal Medicine.

A Post-War Program for the American College of Physicians

At a meeting of the Board of Regents of the College at its headquarters in Philadelphia, June 10, 1945, much time was devoted to the consideration of a special educational program connected with the post-war planning of the College. The detailed minutes will be published in the next issue of this journal.

The Board of Regents proposed to employ an Educational Director to work under the Executive Secretary. The proposed programs of the Committee on Fellowships and Awards, the Advisory Committee on Postgraduate Courses, the Committee on Educational Policy and the Committee on Post-War Planning for Medical Service will be correlated. One of the chief aims of this program will be to offer assistance to members of the College returning from active military service. The program of Postgraduate Courses, both of the short refresher and longer review types, will be considerably multiplied in 1946; a service will be initiated to help College members returning from the war to locate residencies, assistantships, teaching appointments, or places of practice. The College will resume granting four or five annual Research Fellowships and a sum of $25,000 has been appropriated for the establishment of Clinical Fellowships.

The American College of Physicians has the machinery ready, from several years of experience, to administer this extended program. Its aim is to offer to its members a personalized, intelligent and effective service. No medical society has a more honored and respected reputation for effective work in the educational field. It is hoped that foundations and some of the leading manufacturers of pharmaceuticals and medical supplies and publishers may wish to assist in this program by making grants to the College so that the maximum objectives may be attained.

It should be understood, however, that the College will continue to participate in the activities of the central Committee on Post-War Medical Service, consisting of the American College of Surgeons, the American Medical Association, the American College of Physicians and several other agencies. The central committee, meeting monthly at Chicago, is conducting a most worthy national program, perhaps of a less specific character, but more along the line of public relations and national principles. The minutes of the national Committee on Post-War Medical Service are not at this time repeated in this journal because they have been published recently in the Journal of the American Medical Association.

War-Time Graduate Medical Meetings

Region No. 1 (Maine, New Hampshire, Vermont, Massachusetts) and Region No. 2 (Connecticut, Rhode Island)—New England Committee for War-Time Graduate Medical Meetings—Dr. W. R. Ohler, Chairman; Dr. L. E. Parkins, Secretary; Dr. S. B. Weld, Dr. A. M. Burgess, Dr. C. S. Keefer, Dr. F. T. Hill, Dr. J. P. Bowler, Dr. B. F. Cook, Executive Committee members.

Station Hospital, Dow Field, Bangor, Maine

July 17 Fractures of Extremities and Pelvis. Joint Injuries.
August 21 Pilonidal Sinus and Common Diseases of the Anus and Rectum.

Dispensary, U. S. Naval Air Station, Brunswick, Maine

July 19 The Use of Penicillin and Sulfa Drugs.
August 16 Recent Advances in Diagnosis and Treatment of Diseases of the Central Nervous System.

Station Hospital, Fort Williams, Portland, Maine

July 19 Acute Abdominal Emergencies.
August 16 Acute Hepatitis: Its Diagnosis and Treatment (Pathological Physiology).

Station Hospital, Presque Isle, Maine

July 19 Hypertensive Cardiovascular Disease; Rheumatic Heart Disease, Treatment and Rehabilitation.
August 16 Diagnosis and Medical Treatment of Biliary Tract Lesions. Surgical Treatment of Biliary Disease.

Station Hospital, Grenier Field, Manchester, New Hampshire

July 18 Diagnosis and Medical Treatment of Biliary Tract Lesions. Surgical Treatment of Biliary Disease.
August 15 Diagnosis and Treatment of Skin Diseases.

U. S. Naval Hospital, Portsmouth, New Hampshire

July 19 Diagnosis and Treatment of Skin Diseases.
August 16 Recent Advances in the Treatment of Mental Diseases and Management of Psychoneuroses.

Regional Hospital, Waltham, Massachusetts

July 19 Tumors of the Central Nervous System and Neurological Syndromes.
August 16 Cardiac Emergencies, Diagnosis and Treatment.

U. S. Naval Hospital, Chelsea, Massachusetts

July 19 Diagnosis and Treatment of Skin Diseases.
August 16 Cardiac Emergencies, Diagnosis and Treatment.

Lovell General Hospital, Fort Devens, Massachusetts

July 19 Blood Transfusions, Whole Blood and Derivatives, and the Rh Factor.
August 16 Acute Abdominal Emergencies.

Station Hospital, Camp Edwards, Massachusetts

July 19 Cardiac Emergencies, Diagnosis and Treatment.
August 16 Contagious Diseases and Complications.

Cushing General Hospital, Framingham, Massachusetts

July 19 Acute Infections of the Central Nervous System.
August 16 Fractures of Extremities and Pelvis. Joint Injuries.

Station Hospital, Camp Myles Standish, Taunton, Massachusetts

July 19 Pilonidal Sinus and Common Diseases of the Anus and Rectum.
August 16 Thyroid, Pituitary and Adrenal Diseases. Ovarian and Testicular Hormones Therapy.

U. S. Marine Hospital, Brighton, Massachusetts

July 19 Diagnosis and Medical Treatment of Gastric Lesions. Surgical Treatment of Gastric Lesions.
August 16 Skull Fractures. Injuries to Spine.

Station Hospital, Westover Field, Chicopee Falls, Massachusetts

July 19 Recent Advances in the Treatment of Mental Diseases and Management of Psychoneuroses.
August 16 Thrombophlebitis and Emboli. Vascular Surgery.

Dispensary, U. S. Naval Construction Training Center, Davisville, Rhode Island

July 19 Burns and Reconstruction Surgery.
August 16 Blood Dyscrasias.

U. S. Naval Hospital, Newport, Rhode Island

July 19 Thyroid, Pituitary and Adrenal Diseases. Ovarian and Testicular Hormone Therapy.
August 16 Burns and Reconstruction Surgery.

Station Hospital, Bradley Field, Windsor Locks, Connecticut

July 19 Arterial Disease. Inflammatory Arterial Disease.
August 16 Diagnosis and Medical Treatment of Gastric Lesions. Surgical Treatment of Gastric Lesions.

U. S. Naval Submarine Base, New London, Connecticut

July 19 Contagious Diseases and Complications.
August 16 The Use of Penicillin and Sulfa Drugs.

Region No. 14 (Indiana, Illinois, Wisconsin)—Dr. W. O. Thompson, Chairman; Dr. N. C. Gilbert, Dr. W. H. Cole, Dr. W. D. Gatch, Dr. R. M. Moore, Dr. H. M. Baker, Dr. E. R. Schmidt, Dr. E. L. Sevringhaus, Dr. F. D. Murphy.

Gardiner General Hospital, Chicago, Illinois

July 18 Bone and Joint Infections.
July 25 Arterial Vascular Disease—Traumatic Lesions.

Station Hospital, Fort Sheridan, Illinois

July 18 Repair of Bone in Fractures and Diseases.

Vaughan General Hospital, Hines, Illinois

July 18 Laboratory Diagnosis and Its Relationship to Medical and Surgical Treatment.
July 25 Conditions Affecting Glucose Metabolism.

Mayo General Hospital, Galesburg, Illinois

July 18 Blood Dyscrasias, Malaria, Filariasis.
July 25 High Blood Pressure.

Station Hospital, Chanute Field, Illinois

July 18 Mental Hygiene and the Prevention of Neuroses in War.
July 25 Thrombosis, Thrombophlebitis and Anticoagulants in Less Common Peripheral Vascular Diseases.

Station Hospital, Camp McCoy, Wisconsin

July 18 Plexus and Peripheral Nerve Injuries.
July 25 Dermatological Diseases.

Station Hospital, Truax Field, Wisconsin

July 18 Endocrinology.
July 25 Virus and Rickettsial Diseases—Medical and Neurological Diseases and Treatment.

Billings General Hospital, Indiana

July 18 Peptic Ulcer, Gall Bladder and Liver Diseases.
July 25 Low Back Pain.

Wakeman General Hospital, Camp Atterbury, Indiana

July 18 Chest Diseases and Diseases of the Larynx.
July 25 Bone and Joint Infections.

REGION No. 23 (Nevada, Northern California)—Dr. S. R. Mettier, Chairman; Dr. E. H. Falconer, Dr. D. N. Richards.

Dibble General Hospital, Menlo Park, California

August 6 Coronorary Diseases: Diagnosis and Management—Dr. Edwin L. Bruck. Rheumatic Fever—Lieutenant Maurice Sokolow.

REGION No. 24 (Southern California)—Lt. Comdr. Geo. C. Griffith, Chairman; Capt. H. P. Schenck, Dr. J. F. Churchill, Dr. W. A. Morrison, Maj. N. Nixon.

Birmingham General Hospital, Van Nuys, California

July 25 Surgery of the Traumatic Urinary Tract—Lieutenant Commander Carl Rusche.

A.A.F. Regional Hospital, March Field, Riverside, California

July 17 Communicable Disease—Major Norman Nixon and Captain Charles D. Marple.

Station Hospital, Camp Cooke, Lompoc, California

July 18 Plastic Surgery in Defects of the Head and Neck—Dr. Edward Lamont.

U. S. Naval Air Training Station, San Diego, California

July 20 Classification and Diagnosis of Anemias—Dr. Alvin Foord.

Hoff General Hospital, Santa Barbara, California

July 18 Plastic Surgery in Defects of the Head and Neck—Dr. Edward Lamont.

A.A.F. Regional and Convalescent Hospital, Santa Ana Army Air Base, California

July 17 Wound Healing—Major Walter Birnbaum.

U. S. Naval Hospital, Santa Margarita Ranch, Oceanside, California

July 26 Management of the Diabetic Patient—Dr. John Sherrill.

U. S. Naval Hospital, Long Beach, California

July 18 Penicillin in Syphilis and Gonococcic Infections—Lieutenant Commander W. Duemling.

U. S. Naval Hospital, Corona, California

July 26 Thyroid Disease—Lieutenant Commander George Crile, Jr.

LETTER TO THE AMERICAN COLLEGE OF PHYSICIANS FROM

MAJOR JAMES G. BRUCE, (MC), U. S. ARMY

(ASSOCIATE OF THE AMERICAN COLLEGE OF PHYSICIANS),

RECENTLY LIBERATED FROM BILIBID PRISON, MANILA

"On May 1, 1941, my initial active duty was at Fort Ethan Allen, Vermont, where I was Chief of the Medical Service and Acting Commanding Officer for a short period. Duty in this country was short-lived and I sailed for Manila on August 9, 1941. There I was assigned to the Sternberg General Hospital and became Head of the General Medical Section under Major J. O. Gillespie, F.A.C.P., who was the Chief of the Medical Service. Major Gillespie later commanded another hospital on Bataan, at which time he became a full Colonel. After we were captured by the Japanese, he, being a Colonel, was taken immediately to Formosa with the other Colonels and Generals.

"After Pearl Harbor, our general medical wards at Sternberg were converted to surgical wards in order to cope with large numbers of bombing casualties. From December 12 to December 25 I was Executive Officer of one of the annexes of Sternberg General Hospital. We had only ten Filipino doctors and practically all Filipino help. We had 300 beds designated to take medical cases only; all surgical and casualty cases were to go to Sternberg or some other annex. This also was short-lived; the Japanese were nearing Manila. On December 25 orders came to evacuate the patients, beds, medical supplies and equipment to Bataan. We sailed for Bataan on Christmas night.

"On Bataan I was assigned to General Hospital No. 1, designated as Chief of the Medical Service, carrying on also one medical ward. The medical service was light, but we were short of doctors. On January 25, 1942, this hospital was moved to the rear and I was transferred to General Hospital No. 2. Here, unlike Hospital No. 1, there were no buildings; our patients occupied beds in the jungle, right out in the open. I had a minor surgical ward and was kept busy aplenty. From this time until the fall of Bataan, malaria and dysentery rose in incidence and almost every casualty needed medical treatment to supplement the care of his battle wound.

"At the fall of Bataan on April 9, 1942, we were ordered by the Japanese to keep on in the treatment of our hospital cases. They did not touch the medical or pharmacy supplies, but to our dismay they hauled away all of our food supplies, except rice. They also surrounded our hospital area with artillery batteries and began firing on Corregidor. Our counter batteries from Corregidor were accurate and only one shell fell in the hospital area, and the casualties were few.

"The Japanese closed this hospital on May 26, 1942 (everyone was cured by edict) and our hospital personnel was sent to Cabanatuan (via a four-day stopover in Bilibid Prison at Manila). At Cabanatuan, Prison Camp No. 1, we established a hospital as best we could, using the medicine and instruments we had carried in on our backs. By this time, Americans at this camp were dying at the rate of fifteen to fifty per day; water was scarce; food consisted of rice and a thin vegetable soup; sanitation was nil and the rainy season was on. About all we could do was to identify the dead and reassure the living.

"Later, in 1943, our slant-eyed hosts decided to give us a livable diet with fresh meat and brought in a few critical items such as quinine, aspirin, emetin, and gave us a microscope to use. The boys ceased to die, but we had lost 2,600 in the first six months of camp.

"I was most fortunate to remain as a ward officer in this hospital throughout 1943 and most of 1944. There was a diphtheria epidemic, which subsided spontaneously. The Japanese finally furnished us with antitoxin in sufficient quantities, just as the epidemic was subsiding. It is interesting to note there were cases involving the larynx, conjunctiva, penis, and several cases were followed by paralyses. Our dysentery area at one time in late 1943 contained 1200 cases with positive stools for ameba. Ninety per cent of all patients at one time or another presented symptoms and signs of at least one vitamin deficiency such as zerophthalmia with corneal ulcer, beriberi in all its forms, massive edema, scurvy, ariboflavinosis or pellagra. It is regrettable that research work could not be carried out on this abundance of clinical material, but it was impossible with no laboratory (except a microscope and two pipettes), with little or no medicine, especially vitamins, and no paper to work with except the backs of milk can labels and cigarette packages, which were used for clinical records.

"In January of 1944, the Japanese told us that since we had Red Cross food packages (the Gripsholm also brought drugs, shoes, toilet articles and other items) they would stop our killing carabao for fresh meat. They reduced the rice ration from 550 grams per day to 400 grams per day. This was only the first cut. Later it went to 300 grams, then 200 grams per day; and when the Yanks came in, the diet was at 150 grams per man per day. Everyone began to lose weight. Items which previously could be purchased in the commissary became unobtainable or out of reach in price due to inflation (officers were paid in Japanese script or invasion money, which we called Mickey Mouse money). Patients who had overcome their vitamin deficiencies in 1943 now were again burdened with beriberi and pellagra. Many of us started little gardens of our own, but the only vegetables that could be raised on the soil of that area without fertilization were okra and egg plant.

"On September 21, 1944, I had the biggest thrill of my life. American planes flew over, a beautiful sight, not just a few like the Japs fly, but literally hundreds of them, looking like a great flock of geese. On returning from their mission, two planes left formation, flew low over camp, dipped their wings and cleared their guns. At last Americans had returned after more than two years of waiting! From that time on we saw many planes. Our guards were quite disgusted. We always went out to see them, but the Japs dove into their previously prepared foxholes and forgot about their sentry posts, even if the flight was miles away.

"In October, 1944, I was fortunate to be picked by the Japanese to join a detail of ten medical officers and sixty-five corpsmen destined for Bilibid Prison in Manila to take over the hospital there. A similar detail was picked to remain at Cabanatuan and the excess of the medical personnel from both places was evacuated to Japan with the 'healthy' (so-called by the Japs) prisoners.

"Bilibid Prison, built by the Spanish, made livable by the Americans in the early 1900's, is the place where Walker did his famous work on amebae, differentiating

histolytica from coli, using convicts for clinical material. It is not a pleasant place, being surrounded by thick stone walls twenty-five feet high, but to us it afforded running water in plenty from the Manila city supply and automatic flush straddle trenches, the latter built in 1942 by the ingenuity of American prisoners of war. Sanitation was no longer a problem.

"The real problem at Bilibid, however, was food. The Japs claimed it was hard to get food into Manila because of lack of transportation. Whatever the reason, we did not get it and the patients suffered. A diet of 1,000 calories—150 grams of rice, 50 grams of cornmeal and 50 grams of soy beans, was not enough. It not only was unbalanced, but lacked vitamins; it was difficult for a dysentery case to digest. Wood also was rationed and, coupled with lack of cooking facilities in the kitchen, it was impossible to get out more than two meals per day. Our mess officer inveigled some canned milk from the Japs, which was used up a few weeks before the Yanks came in. This milk was used on the severe malnutrition cases. Many patients lacked clothes, blankets and bedding. There were beds only for those who were critically ill. The remainder lay on mattresses, or nothing at all on the concrete floor.

"Each medical officer at Bilibid had an administrative job, as well as professional duties. I was Executive Officer and Registrar, besides having one ward and being Chief of the Medical Service. Fortunately, we were all in good condition when we left Cabanatuan and our stay at Bilibid was interrupted by General MacArthur and his troops.

"On February 4 of 1945 the Jap guards left the compound at 1:30 p.m., leaving a note in English stating that we were free, but that we should not leave the compound and that they, the Japanese, were called on another mission. Five hours later there was a tap on a boarded-up window in one of the outside walls. Our patients tore down the boards and there they were, face to face with a group of American soldiers and their officers. A yell went up like that after the winning touchdown at a football game! We could not believe we were back under the American flag, but good old American food, with plenty of coffee, sugar, milk and butter soon convinced us.

Sincerely yours,

JAMES G. BRUCE, Major, (MC), U. S. Army
(formerly Springfield, Mass.)"

(Editor's Note: Dr. Bruce during his imprisonment was a Captain. He has been promoted to Major as of February 23, 1945, and according to recent press releases has been voted the Legion of Merit from General MacArthur. He has regained his strength and also thirty-five pounds in weight, lost while in Bilibid Prison. He reported to the Lovell General Hospital, Fort Devens, Mass., on April 22 for medical observation and on May 3 was released on thirty days sick leave. He will report back to Lovell General Hospital on June 7, following which he will probably receive sixty days regular leave. In late August he will be reassigned to duty. Two other members of the College, Lieutenant Commander William M. Silliphant, (MC), U. S. Navy, and Lieutenant Commander J. LaMonte Zundell, (MC), U. S. Navy, also liberated from Bilibid Prison, were patients of Major Bruce at time of liberation.)

OBITUARY

DR. CHARLES HENRY LAWRENCE

Dr. Charles Henry Lawrence of Boston, Fellow of the College, died on March 13, 1945, following a coronary artery thrombosis. He was born on October 17, 1882, in Chicago. Following his precollegiate training in Illinois, he entered Harvard College and was graduated in 1904, although he had earned his A.B. *cum laude* a year earlier. In 1908, he was granted the degree of M.D. from the Harvard Medical School, and then served as a house officer at the Massachusetts General Hospital. From 1911 to 1917, he held various appointments at the Massachusetts General Hospital and the Harvard Medical School. During World War I he served as a First Lieutenant in the Medical Corps, U. S. Army, and following the war he was appointed physician at the Evans Memorial Hospital of the Massachusetts Memorial Hospitals, a position which he held with distinction until 1934 when he became Chief of the Endocrine Clinic of the Boston Dispensary and attending physician at the New England Medical Center. From 1934 until 1945, he was also an instructor and assistant professor of medicine at Tufts Medical School.

In 1911, Dr. Lawrence married Miriam Oliver Williams of Plymouth, Massachusetts. They had four sons, Charles Henry 3rd, Edward Williams, David Bissell, and George Hugh.

At the time of his death Dr. Lawrence held the following positions: assistant professor of medicine, Tufts College Medical School; physician-in-chief of the Endocrine Clinic and consulting physician of the Children's Clinic, New England Medical Center; member of Associate Staff, Faulkner Hospital; consulting physician, Charles Choate Memorial (Woburn) and Symmes Arlington Hospitals; consultant in endocrinology, Joseph H. Pratt Diagnostic Hospital. He was a member of the following societies: Massachusetts Medical Society, Society for the Study of Internal Secretions, and American Clinical and Climatological Association; Aesculapian Club; Fellow, American Medical Association, and Fellow, American College of Physicians since 1929.

His friends and associates had a high regard for his professional ability and character. Aside from his profession he was interested in music, religion, and sailing.

No greater tribute can be made than a quotation from one of his close friends and colleagues. "I can testify that for intellectual honesty, devotion to the good of his fellowmen, broad, understanding charity of outlook towards all, and complete selflessness he stands out as a real, practising Christian gentleman."

All men who knew Dr. Lawrence will miss him as a loyal friend, an excellent doctor and clinical investigator.

CHESTER S. KEEFER, M.D., F.A.C.P.,
Governor for Massachusetts